SYNTHESIS AND CHARACTERISATION OF CYCLAZINES

William David Smith, B.Sc.

A Thesis presented for the degree
of Doctor of Philosophy

University of Edinburgh

August 1987

Abstract

The investigation was centred on the chemistry of pyrido[2.1.6-de]quinolizines ([3.3.3]cyclazines) and some related bi- and tri-cyclic quinolizine derivatives.

A new and more efficient route to [3.3.3]cyclazines was developed starting from 4-chloroquinolizinylium perchlorate and carbanions derived from activated propenes. This method, which yielded diethyl [3.3.3]cyclazine-1,3--dicarboxylate in 83% yield in a "one-pot" synthetic procedure, was used to prepare a number of [3.3.3]cyclazines bearing electron-withdrawing substituents in the 1- and 3-positions. Experiments aimed at the synthesis of [3.3.3]-cyclazines from quinolizin-4-thiones are also described.

The reactions of diethyl [3.3.3]cyclazine-1,3-dicarboxylate were further investigated. Cycloaddition products were obtained by reaction with various olefinic and acetylenic dienophiles but azodicarboxylates caused substitution in the cyclazine nucleus rather than cycloaddition. Reactions with benzyne and with ethoxycarbonyl carbene are also described. Oxidation of the diester with a variety of reagents gave [2.3.3]cyclazinone derivatives and a series of novel oxo[3.3.3]cyclazinium-olates in varying yields. The unusual oxidative extrusion of one carbon atom to form [2.3.3]cyclazinones was also observed for the parent [3.3.3]cyclazine. An attempt to form a charge-transfer complex of the [3.3.3]cyclazine diester with tetracyanoquinodimethane gave a product in which two cyclazine moieties were covalently linked to a tetracyano-

-p-xylene residue.

Some attempts to use flash vacuum pyrolysis to synthesise aza[3.3.3]cyclazines from 4H-quinolizin-4-ylidene precursors are described. These experiments led, in one case, to the formation of 2-cyano-[2.3.3]cyclazin-1-one and, in another case, to the discovery of a novel rearrangement of quinolizin-4-ylidenemalononitrile to give 5-(dicyanomethyl)-quinoline.

Finally, a route to [2.3.3]cyclazin -3- and -5-ones from 1- and 3-hydroxyquinolizinylium salts and activated acetylenes was improved by the use of phenanthraquinone as a dehydrogenating agent. In one case some interesting byproducts were formed by coupling of a [2.3.3]cyclazinone moiety with the quinone, and their structures were elucidated by n.m.r. spectroscopy.

Postgraduate Courses

The following is a statement of postgraduate courses attended at Edinburgh from October 1983 to September 1986.

"Organo-Silicon compounds - Preparation, properties and utility in synthesis"	Dr. W.E. Colvin (University of Glasgow)
"Synthetic strategy"	Professor R. Ramage (University of Edinburgh)
"Molecular Electronics"	Professors R.W. Munn and J.D. Williams (University of Manchester Institute of Science and Technology)
"Microcomputers and Instrumentation"	Dr. A. Rowley, Mr. A. King and Mr. C. Adie
"Chemical Technology and Industrial Chemistry"	Drs. Nicoll, Mustoe and Sinclair
"X-ray crystallography"	Dr. O. Kennard, Dr. G. Watson S.A. Bellard, F.H. Allen (Cambridge University) and Dr. T. Brown (University of Edinburgh)
"N.m.r. spectroscopy"	Dr. I.H. Sadler (University of Edinburgh)

"Medicinal Chemistry"	Drs. L.R. Hughes and A.G. Brewster (ICI Pharmaceuticals); Dr. J.D.R. Vass (ICI, Grangemouth); and Drs. J.P. Clayton and I.Francois (Beecham Pharmaceuticals)
"Current topics in organic chemistry"	A series of lectures given by various lecturers of the University of Edinburgh and by invited lecturers

Attendance at seminars and colloquia over the three years.

For my family and for Morag.

Acknowledgements

I wish to take this opportunity to thank Dr. Derek Leaver for his constant guidance and encouragement throughout the course of this work. I am also indebted to the staff of the Chemistry Department, University of Edinburgh, for the efficient provision of various services.

Finally, I wish to thank the University of Edinburgh for the provision of laboratory facilities, the S.E.R.C. for a research studentship and Mrs. R. Filipiak for her skillful and patient typing of this manuscript.

Contents Page No.

SECTION I

INTRODUCTION

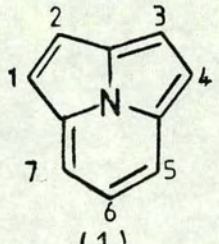
SECTION 1

INTRODUCTION

1. The Cyclazines: Definition and Nomenclature

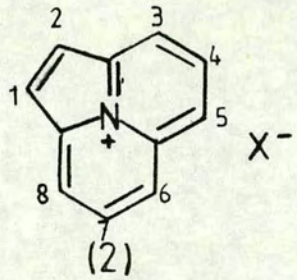
"Cyclazine" was the name originally proposed by Boekelheide[1] in 1958 to describe a family of heterocyclic molecules that are in general conjugated unsaturated cycles held planar by three covalent bonds to an internal nitrogen atom. Such compounds (1-5) are thus derivable from the annulenes by replacement of three inwardly directed hydrogen atoms by the central nitrogen atom.

The individual members of the cyclazine series are distinguished by using a system of nomenclature which specifies the number of atoms in the annulene ring that lie between the points of bonding to the internal nitrogen atom. Hence, structures (1), (3), (4) and (5) would be [2.2.3]cyclazine; [3.3.3]cyclazine; [2.3.4]cyclazine and [3.4.4]cyclazine respectively and structure (2) would be a [2.3.3]cyclazinylium cation. According to a recent modification[2] of the original proposals[1], these numerals are listed in increasing order, so that their sequence starts at the same point and proceeds in the same direction as the I.U.P.A.C. numbering sequence of the peripheral annulene cycle. The systematic fusion nomenclature for these compounds based on I.U.P.A.C.[3] rules, is derived from the largest named nitrogen



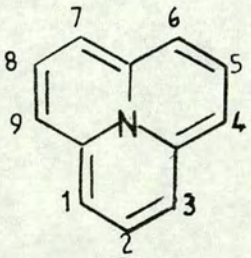
(1)

[2.2.3]CYCLAZINE



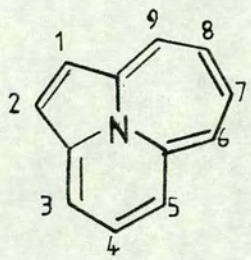
(2)

[2.3.3]CYCLAZINYLIUM ION



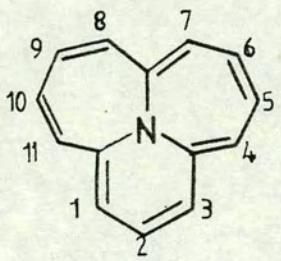
(3)

[3.3.3]CYCLAZINE



(4)

[2.3.4]CYCLAZINE



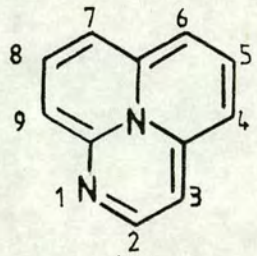
(5)

[3.4.4]CYCLAZINE

FIG.1

containing ring system present within the molecule. Thus, by fusion nomenclature, (1) becomes pyrrolo[2,1,5-cd]-indolizine and (3) would be pyrido[2,1,6-de]quinolizine.

Substitution of a peripheral sp^2 carbon of a cyclazine by a heteroatom, is indicated according to the 'replacement nomenclature' system. For example, (6) would be 1-Aza[3.3.3]cyclazine.



(6)

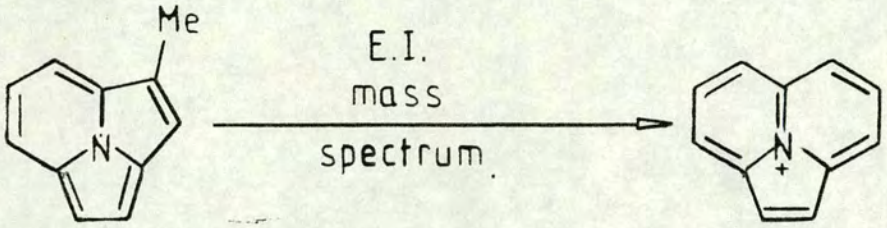
The following review of cyclazine chemistry is restricted mainly to those containing a quinolizine moiety. Several reviews[4] of the other types of cyclazines, including the azaphenalenes[5] are to be found in the literature. These quinolizine related systems form the basis for much of the original research work described here.

2. [2.3.3]Cyclazines (Pyrrolo[2,1,5-de]quinolizines)

Until recently[6], salts of the parent [2.3.3]cyclazinylium ion (2) were unknown, although a number of substituted [2.3.3]cyclazine derivatives had been

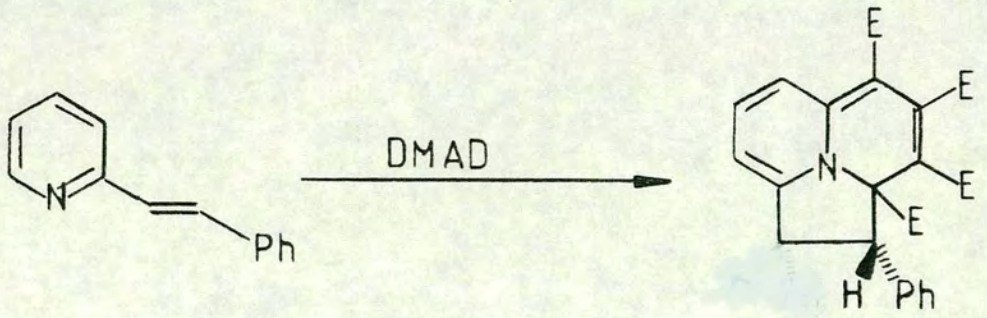
reported.

Acheson and Robinson[7] suggested that the ion observed as the base peak $[M-1]^+$ in the electron impact mass spectrum of 1-methyl[2.2.3]cyclazine (7), might be the [2.3.3]cyclazinylium ion[8]. However, at this stage, no chemical synthesis had been reported. Another earlier reference to the [2.3.3]cyclazine structure relates to the so called 'second stable adduct' (9), derived from



(7) (2)

<u>trans</u>-stilbazole(8) (2-styrylpyridine) and dimethyl acetylenedicarboxylate[9], later shown by Acheson and Feinberg[10] to be a 2a,3,4,5-tetra(methoxycarbonyl)-2-phenyl-1,2-dihydro[2.3.3]cyclazine.

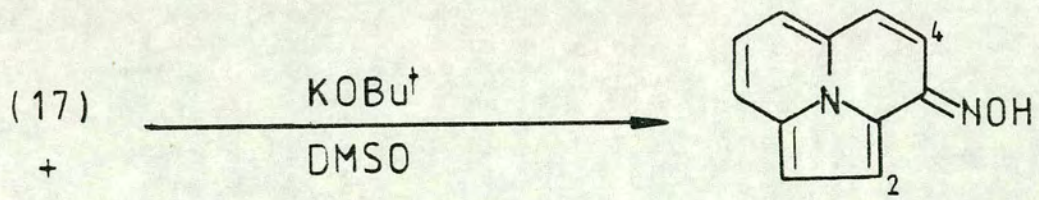


(8) (9)

E = CO_2Me.

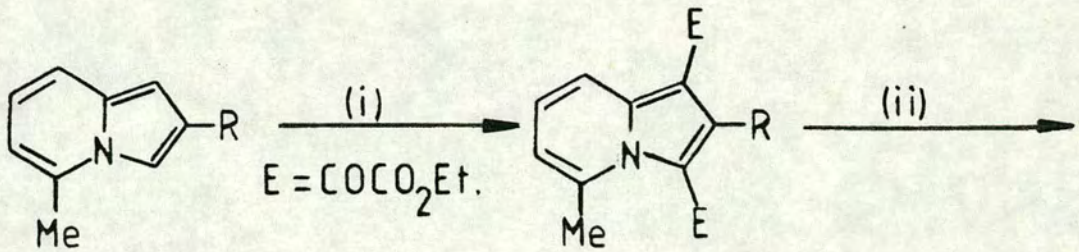
2.1 Synthesis of [2.3.3]cyclazines from indolizines

In the late 1960's, Leaver[11] and his co-workers reported that a hydroxy[2.3.3]cyclazinone (13a) or (14a) could be obtained, together with a [2.2.3]cyclazine derivative (12) by base-catalysed cyclisation of the indolizine (10a) (Scheme 1).



(19)

a: 2-Ph, 4-Me.
b: 2-Me, 4-Ph.
c: 2,4-Ph_2.
d: 2,4-Me_2.

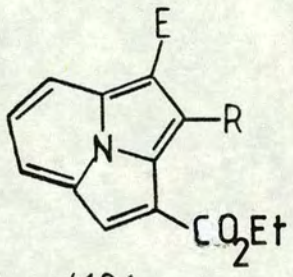


(10)

a : R = Ph.

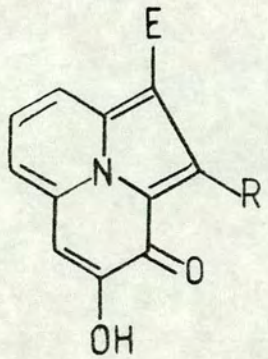
b : R = Me.

(11)



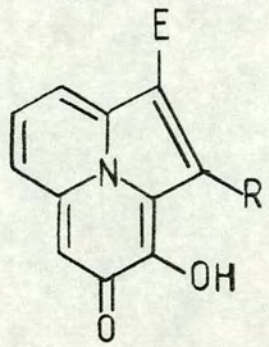
(12)

+



(13)

OR



(14)

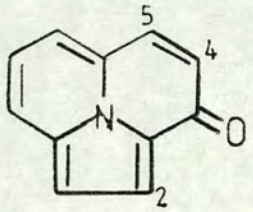
Reagents : (i) Ethoxalyl chloride/CH_2Cl_2.

(ii) $\triangle$ / EtOH / NaOEt.

Scheme 1.

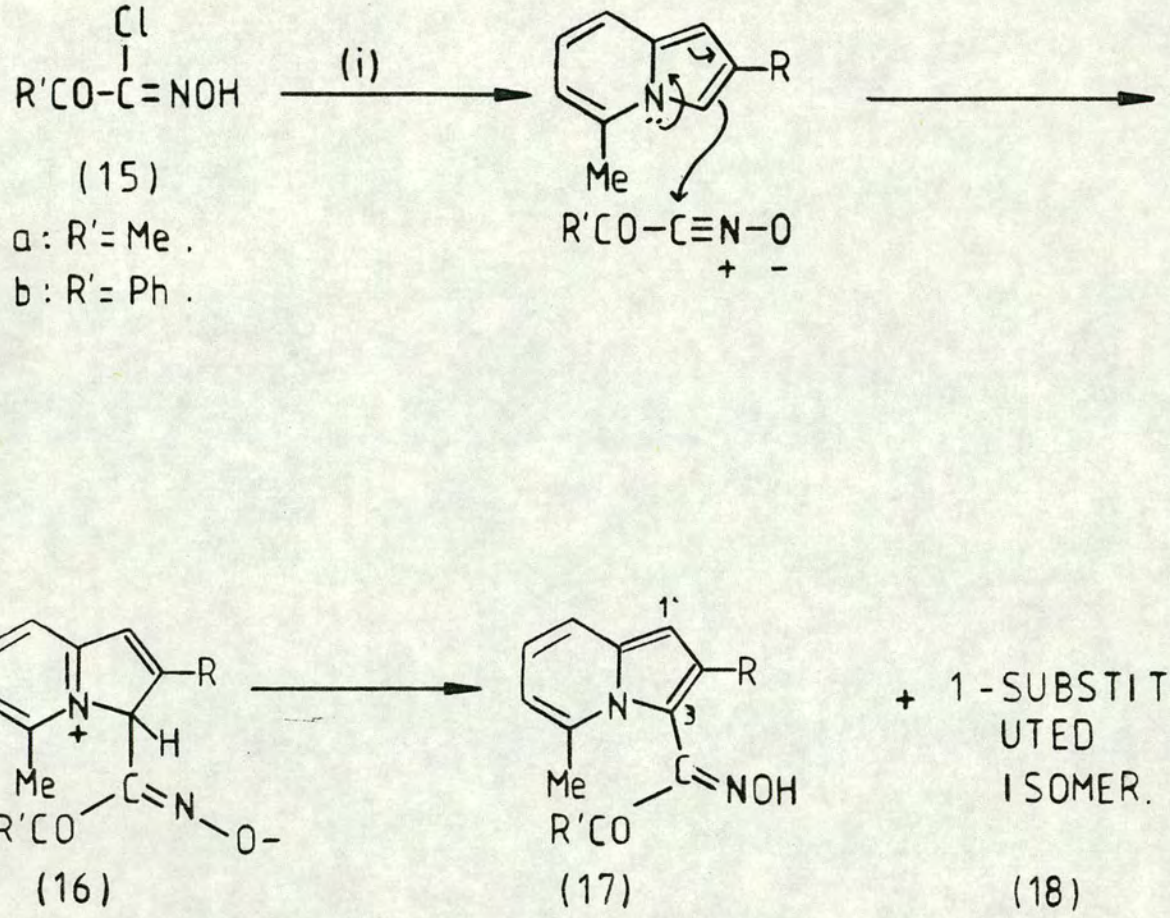
It was later shown[12] that the related hydroxycyclazinone derived from (11b) exists in the tautomeric form (13b) rather than (14b).

In this later publication[12], the synthesis of [2.3.3]cyclazine derivatives from indolizines was further discussed and, in particular, the indolizine starting material was treated with an α-oxohydroximoyl chloride (15), in the presence of triethylamine. This latter reaction was believed to involve a nitrile oxide as the effective reagent (Scheme 2). The intermediate 3-(2-oxohydroximoyl)-indolizines (17/18) were cyclised to the 3-hydroxyimino-3H-[2.3.3]cyclazines, by using potassium tert-butoxide in refluxing dimethyl sulphoxide. These hydroxyiminocyclazines were converted into the corresponding 3H-[2.3.3]cyclazin-3-ones (20) by treatment with silver(I)oxide in refluxing dichloromethane. One of the cyclazinones (20a) was converted by treatment with phosphorus pentasulphide, into



(20)
a: 2-Ph, 4-Me.
b: 2-Me, 4-Ph.
c: 2, 4-Ph_2.

the corresponding cyclazinethione (21), which was methylated to give the [2.3.3]cyclazinylium salt (22).

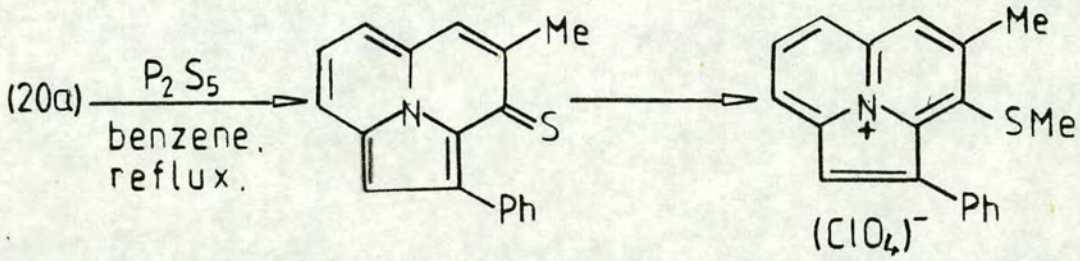


	R	R'
a :	Ph	Me
b :	Me	Ph
c :	Ph	Ph
d :	Me	Me

Reagents :-

(i) $NEt_3/CHCl_3$ / r.t.

Scheme 2 .



(21) (22)

The main disadvantage of the above synthetic routes appears to be the generally low yields in the absence of aryl substituents.

2.2 Synthesis of [2.3.3]cyclazines from quinolizines

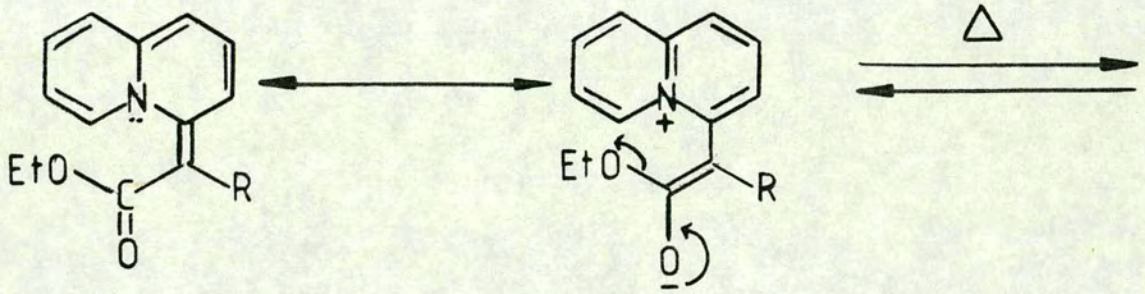
Two alternative routes to [2.3.3]cyclazines starting with quinolizines have been published more recently[6]. Both of these routes are applicable to the synthesis of the parent [2.3.3]cyclazinylium ion (2).

2.2.1 The Cyclisation Route

It was discovered[6] that heating quinolizin-4-ylidene derivatives, such as (23), in high boiling solvents such as nitrobenzene or 1,2,4-trichlorobenzene, caused cyclisation to the corresponding 1H-[2.3.3]cyclazin-1-ones (26) in high yield.

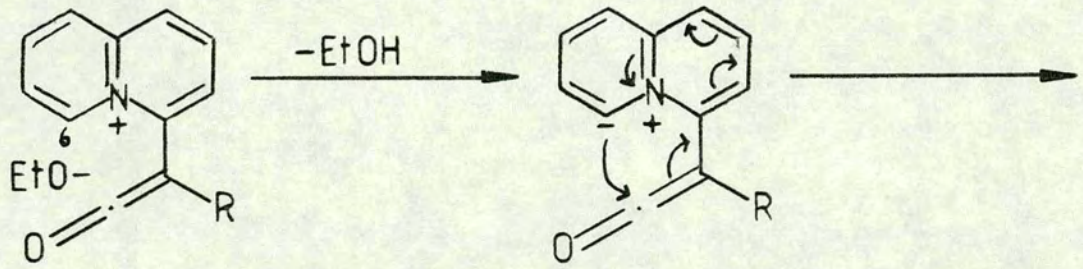
The possible mechanism for such a reaction is discussed, whereby an intramolecular acylation leads to these cyclazinones (Scheme 3).

In view of the contribution of the canonical structure (23c) to the structure of the quinolizine this acylation



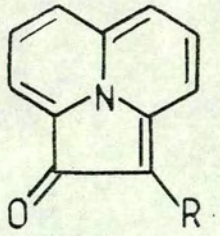
(23)
a: R=CO_2Et.
b: R=CN.

(23c)



(24)

(25)



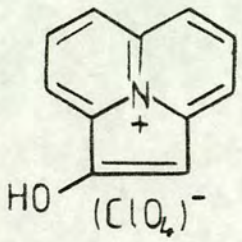
(26)

a: R=H.
b: R=CO_2Et.
c: R=CN.

Scheme 3.

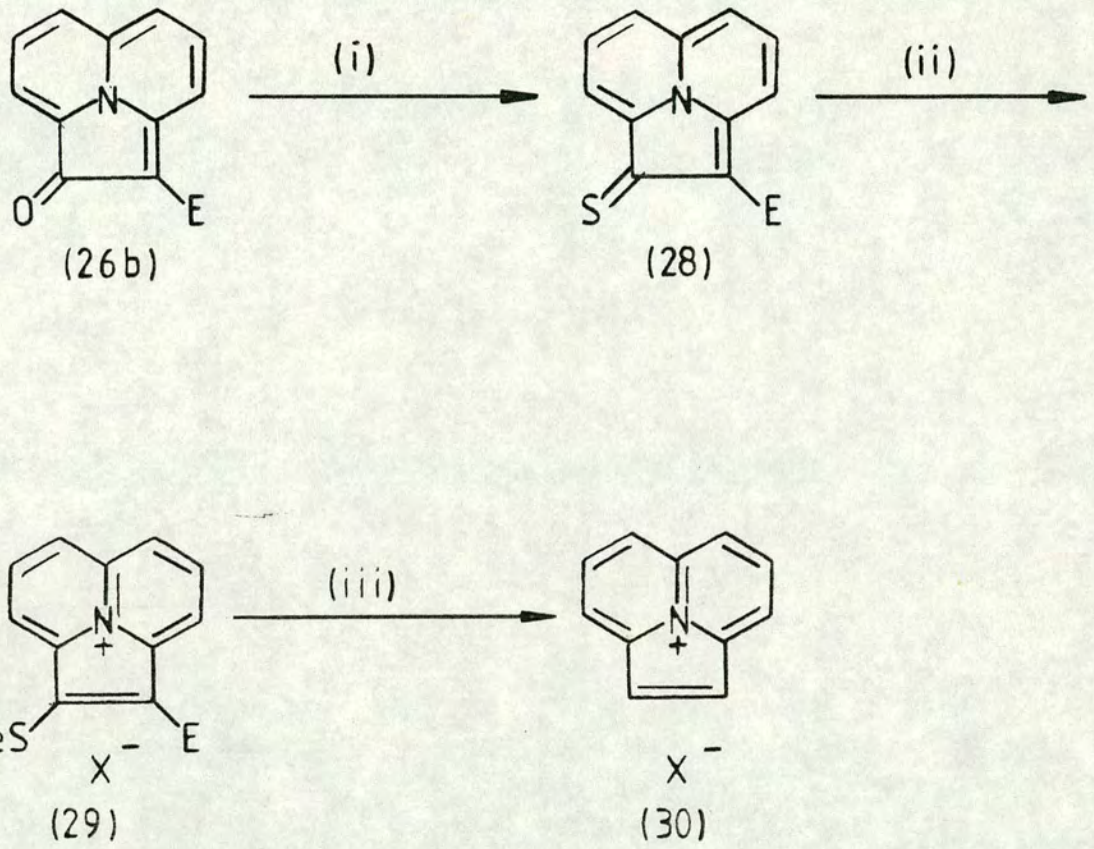
would appear to involve electrophilic attack at a position of low electron density (C-6) within the quinolizine ring system. This apparent anomaly was explained[6] by suggesting that the heating process may lead to an ion pair (24) which features a ketene group at the C-4 position of the quinolizine ring system. The ethoxide anion is then thought to abstract a proton from the C-6 position[14], giving a zwitterion (25). This intermediate contains a σ-carbanion site which would be susceptible to electrophilic attack by the ketene moiety.

The bright red, water soluble parent 1H-[2.3.3]cyclazinone (26a) was obtained in 85% yield by de-ethoxycarbonylation of the ethoxycarbonylcyclazinone (26b), by heating in aqueous hydrochloric acid. The cyclazinone (26a) was easily converted into the 1-hydroxycyclazinylium salt (27) by treatment with perchloric acid.



(27)

The parent [2.3.3]cyclazinylium salt was prepared from the 2-(ethoxycarbonyl)cyclazinone (26b) by converting it firstly into the thione (28) using phosphorus pentasulphide, and methylating with methyl iodide to give the 1-(ethoxycarbonyl)-2-methylthiocyclazinylium salt (29). Subsequent hydrolysis and decarboxylation followed by



(26b) (28) (29) (30)

Reagents :-

(i) P_2S_5.
(ii) MeI.
(iii) a. aq. HCl.
b. Cu_2O / $MeCONMe_2$.
c. Raney nickel.

E = CO_2Et.
X^- = ClO_4^-.

Scheme 4.

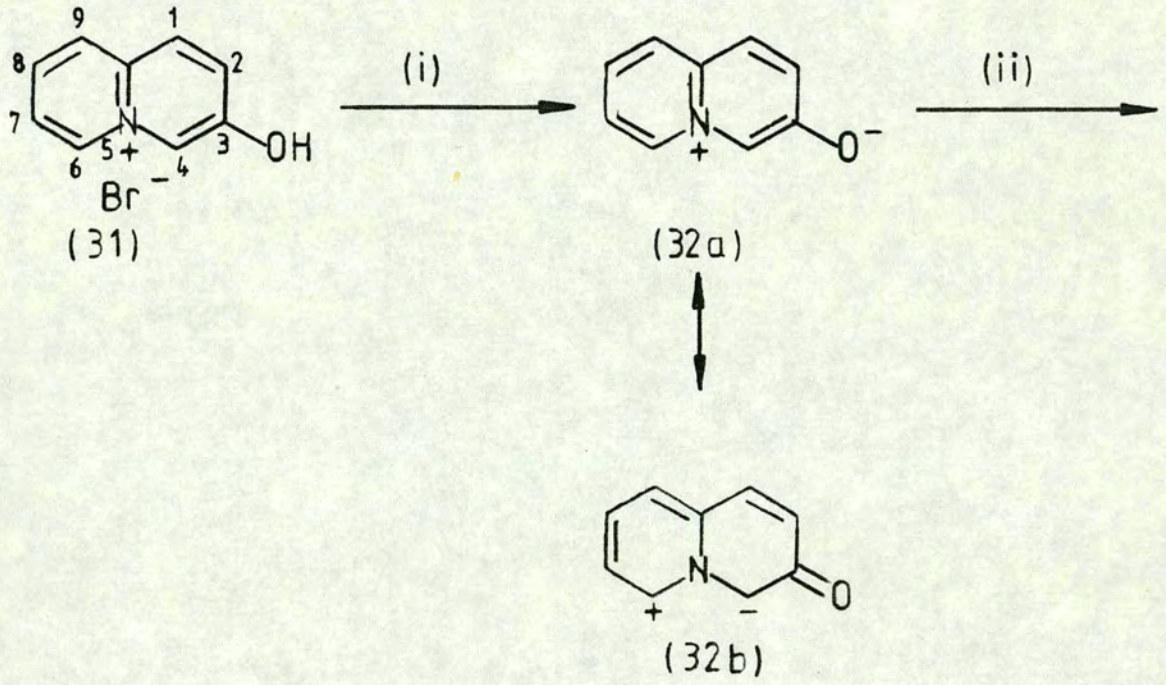
treatment with Raney nickel in ethanol gave the parent salt (30) (scheme 4).

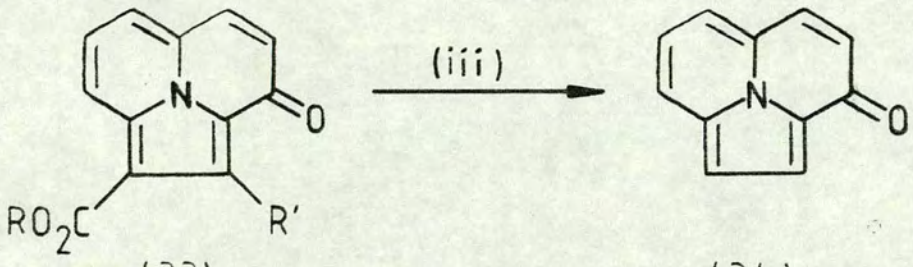
2.2.2 The Cycloaddition Route

A more satisfactory route to the [2.3.3]cyclazinylium ion utilised 3-hydroxyquinolizinylium bromide (31) as the starting material. This salt, when treated with mild base

gives rise to a mesoionic betaine (32), which was expected to exhibit 1,3-dipolar reactivity as represented in the resonance form (32b). Thus, heating of the salt (31) with ethyl propiolate in the presence of anhydrous sodium carbonate in refluxing nitrobenzene, gave rise to a 3H-[2.3.3]cyclazin-3-one derivative (33a). The solvent in this type of reaction also acts as an efficient dehydrogenating reagent. Hydrolysis of the ethoxycarbonyl-cyclazinone and decarboxylation gave the parent 3H-cyclazin-3-one (34) (scheme 5).

A similar synthesis using dimethyl acetylene-dicarboxylate gave rise to a 1,2-di(methoxycarbonyl)-3H-[2.3.3]cyclazin-3-one (33b).





(33) (34)

a: R= Et, R'= H.

b: R= Me, R = CO_2Me.

Reagents :-

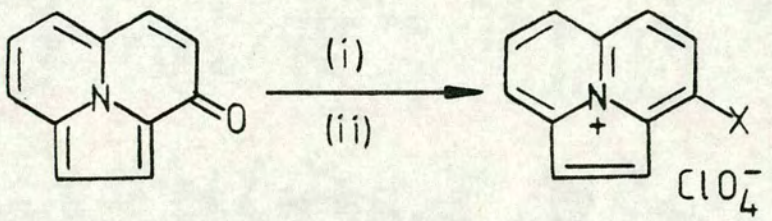
(i) $Na_2CO_3/PhNO_2$.

(ii) $R'-C\equiv C-CO_2R$ / reflux.

(iii) aq. HCl / vac, Cu_2O.

Scheme 5.

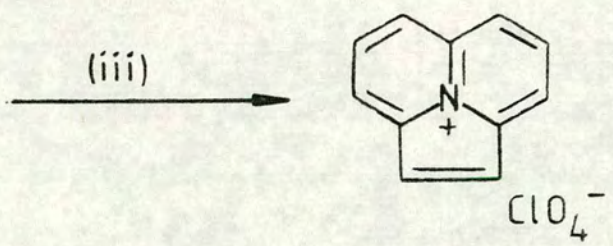
Treatment of the cyclazinone (34) with phosphoryl chloride or bromide gave the corresponding 3-halogeno-[2.3.3]cyclazinylium salts (35) in high yield, and catalytic hydrogenolysis (1 atm H_2, Pd-C) of the 3-bromo salt yielded the parent [2.3.3]cyclazinylium salt (30) in 74% yield[6] (scheme 6).



(34) (35)

a: X = Cl.

b: X = Br.



(30)

Reagents:-

(i) POX_3 (X = Cl, Br).

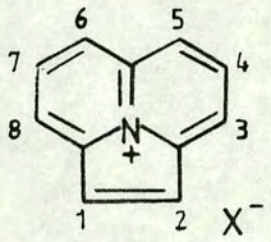
(ii) $HClO_4$/AcOH.

(iii) 1-atm. H_2/Pd-C (for 35b).

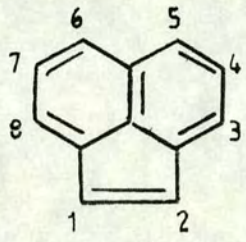
Scheme 6.

2.3 Properties of the [2.3.3]cyclazinylium ion

The [2.3.3]cyclazinylium ion (2) is formally isoelectronic with the hydrocarbon acenaphthylene (35), but differs from it in containing a 1,2-bond which appears to be lacking in olefinic character.



(2)

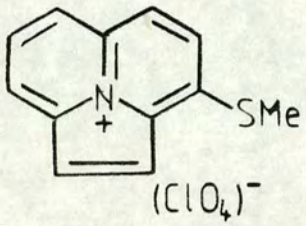


(35)

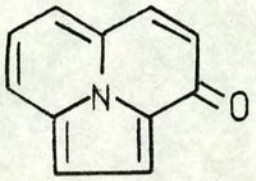
Whereas, the 1,2-bond in acenaphthylene is readily hydrogenated and acts as a dienophile[14,15], the [2.3.3]cyclazinylium salt exhibits neither of these types of reactivity. Evidence from proton n.m.r. studies suggests that the 1,2-bond of the [2.3.3]cyclazinylium ion is more strongly integrated into the aromatic system and that there is a ring current pathway around the whole perimeter of the molecule.

The observation[6] of a third member of the four possible [2.3.3]cyclazinones came from studies on the susceptibility of the parent [2.3.3]cyclazinylium ion (30) to nucleophilic attack. Reaction with sodium sulphide in DMF resulted in a formal displacement of hydride ion to give a mixture of cyclazinethiones which after methylation, yielded a 3-methylthiocyclazinylium salt (36) as the

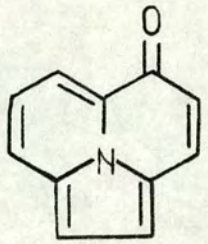
principal product. The presence of two isomeric thiones was revealed by oxidation of the thione mixture in sunlight, to give the 3H-cyclazin-3-one (34) and a small amount of the 5H-cyclazin-5-one (37).



(36)



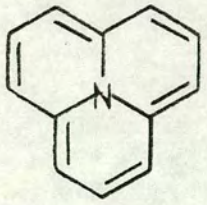
(34)



(37)

[2.3.3]Cyclazin-3-ones or -5-ones were observed in other studies of nucleophilic attack in substituted cyclazinylium salts and as will be discussed later, have also been observed in the current work as oxidation products of [3.3.3]cyclazines.

3. [3.3.3]cyclazines (Pyrido[2.1.6-de]quinolizines)



(3)

After Boekelheide's original predictions[1], based on H.M.O. calculations, that [3.3.3]cyclazine (originally

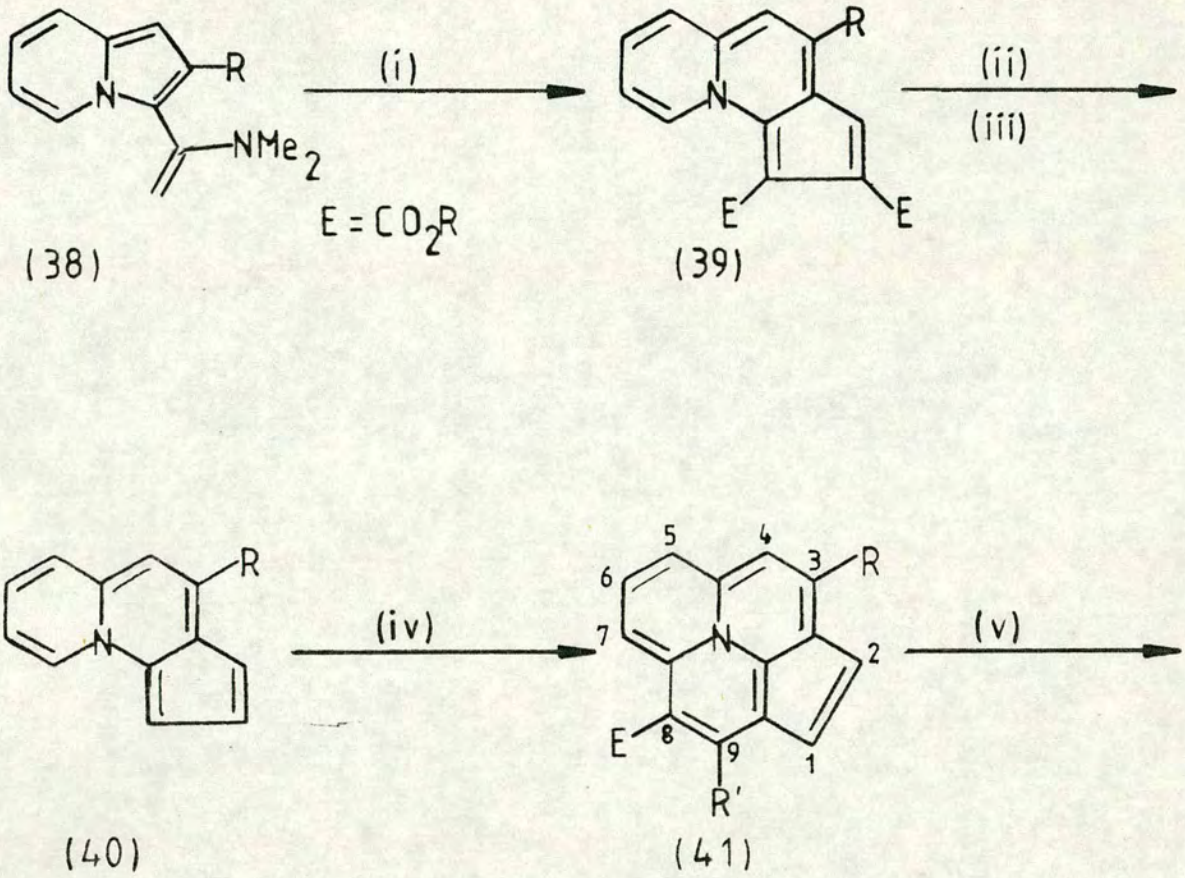
referred to as tricyclazine[16]) would be a stable compound of high resonance energy[1,20], it required more than a decade before a successful synthesis was reported. Several earlier attempts[16-19] to generate the tricyclic system can be seen, in retrospect, to have had little chance of success, [3.3.3]cyclazine being a highly reactive air-sensitive compound. Later calculations[25,26], based on more advanced M.O. methods, have been fully in accord with these observed properties.

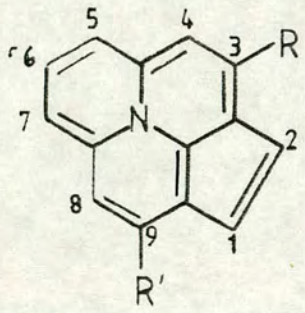
3.1 Synthesis of [3.3.3]cyclazines

In the late 1960's, Leaver reported[21] the synthesis of a cyclopenta[cd]-[3.3.3]cyclazine (41) by reaction of cyclopenta[c]quinolizines[21a] (40) with αβ-acetylenic esters, such as alkyl propiolates. The cyclopenta[c]quinolizines themselves were readily available from 3-(1-dimethylamino-vinyl)indolizines (38) as shown in scheme 7.

The [3.3.3]cyclazine derivatives (42) were judged to be aromatic on the basis of their proton n.m.r. spectra[21b/c]. The chemical shifts showed evidence of diatropicity and the magnitude of the coupling constant $^{3}J_{1,2}$ indicated that the 1,2-bond was part of the aromatic system. Indeed, compound (42) may be considered[21] as a [13]annulenyl anion with weak coupling to a localised azomethinium cross link, as described by structure (43).

Leaver *et al* also reported[22] the synthesis of the parent [3.3.3]cyclazine, and some derivatives, almost a decade and a half after Boekelheide's original proposals. The





(42)

Reagents :-

(i) DMAD / PhMe / △.

(ii) aq. HCl.

(iii) aq. NaOH.

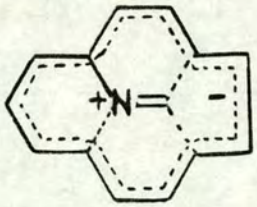
(iv) R'-C≡C-E / $PhNO_2$ / △.

(v) Alkaline hydrolysis / △.

R = H, Ph, Me.

R' = H, Ph, Me.

Scheme 7.

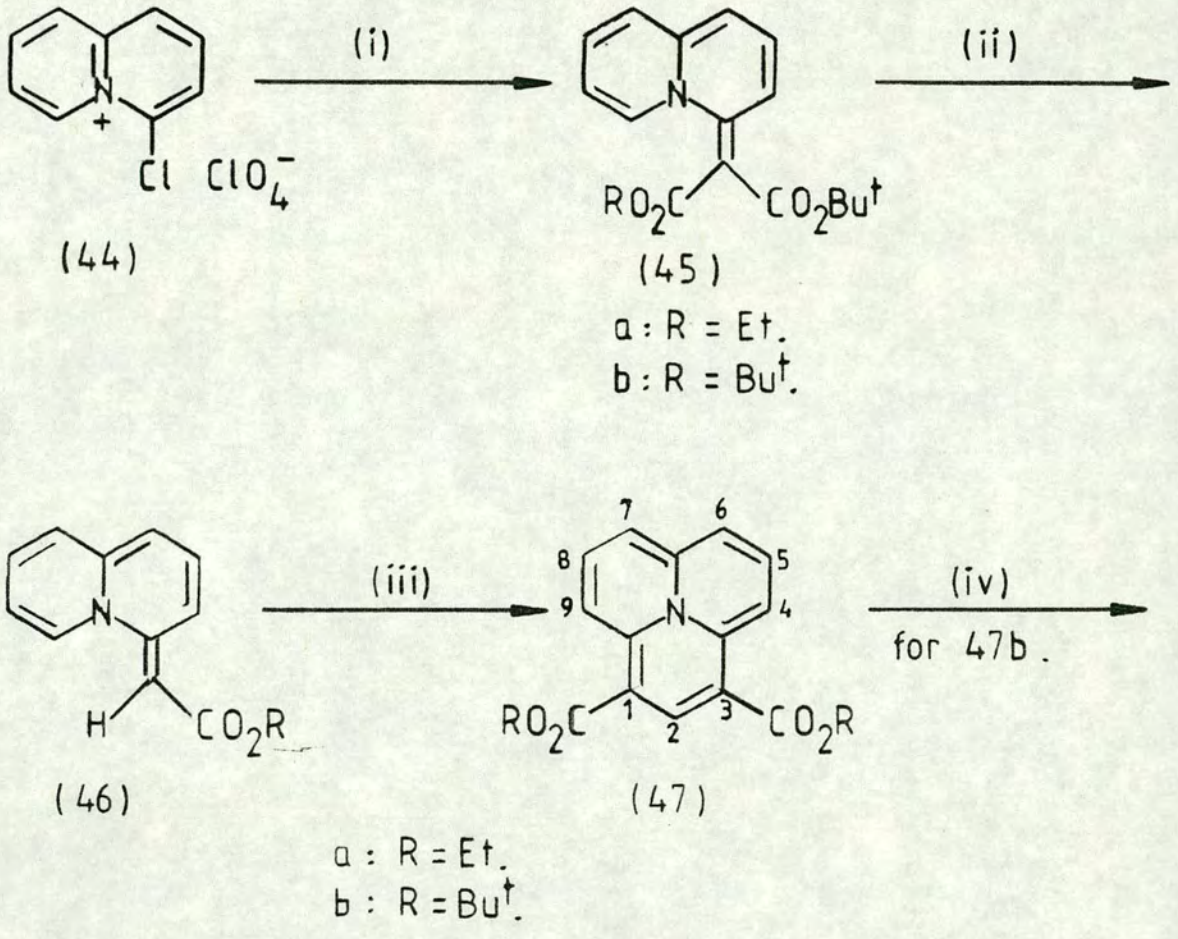


(43)

successful route took advantage of electron-withdrawing substituents to stabilise both the intermediates and the initial cyclazine product, these substituents being removed only in the final step of the synthesis. The route itself is directly analagous to the cyclopenta[3.3.3]-cyclazine synthesis, in that it is also a formal cyclo-addition of an acetylenic ester to a 4-methylene-4H-quinolizine moiety, the adduct being dehydrogenated in situ, with refluxing nitrobenzene, to give the fully unsaturated [3.3.3]cyclazine derivative (scheme 8).

The 4-methylenequinolizines (45) required for this synthesis were obtained by the reaction of 4-chloroquinolizinylium perchlorate (44) with the sodium derivatives of alkyl tert-butyl malonates and the tert-butyl ester group was then selectively removed by hydrolysis and decarboxylation.

The above pathway is essentially a three-stage synthesis of the cyclazine ring system from the quinolizinylium salt (44) and provides the diethyl ester (47a) in 47% overall yield. It suffers from the disadvantage that the intermediates (46) require careful



(44)

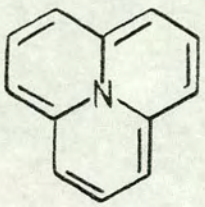
(45)

a : R = Et.
b : R = But.

(46)

(47)

a : R = Et.
b : R = But.



(3)

Reagents :-

(i) $NaCH(CO_2R)CO_2Bu^t$ / THF.

(ii) HCl / PhH (for R = Et) or
$PhSO_3H$ / AcOH (for R = But,
NaOH.

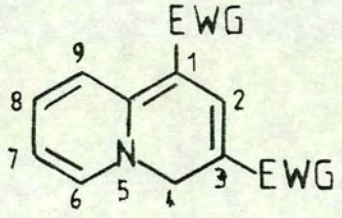
(iii) $H-C\equiv C-CO_2R$ / $PhNO_2$ / 210°C

(iv) For R = But, 270°C / vacuum.

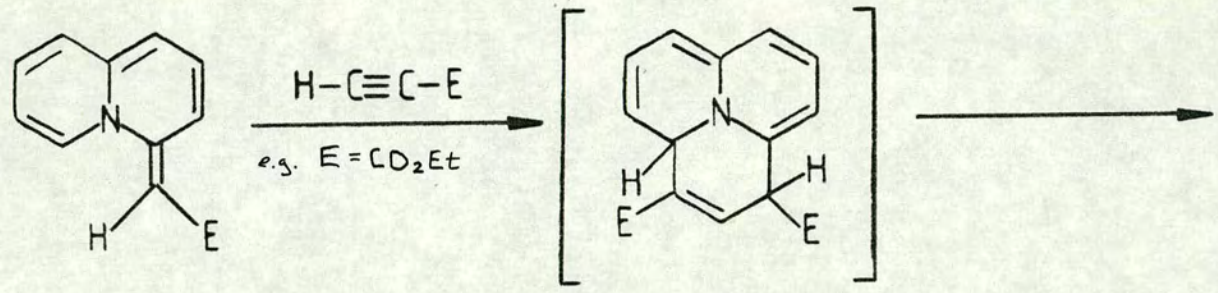
Scheme 8.

handling, because of their air-sensitive nature. A new and superior route to the [3.3.3]cyclazines will be described in the discussion section.

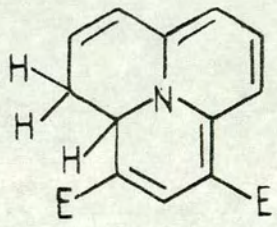
The proposed pathway[22] for this original synthesis involves dihydro intermediates, one of which was isolated as a deep purple solid and identified as the 3a,4-dihydro-[3.3.3]cyclazine derivative (49) (scheme 9).



(50)



(46) (48)



(49)

Scheme 9.

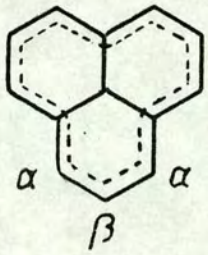
The dihydro intermediate is believed to have been formed from a relatively unstable 1,3a-dihydrocyclazine (48), which is the most probable initial adduct, by hydrogen migration. The higher stability of (49) may be associated with the presence of the 4H-quinolizine substructure, bearing electron withdrawing groups (E.W.G.) in its 1- and 3- positions [structure (50)]. This type of structure is repeatedly found in the chemistry of [3.3.3]-cyclazines, and in other areas[23,24].

The parent [3.3.3]cyclazine (3) was formed from the di-t-butyl ester [(47b)/scheme 9] by thermolysis in a sealed, evacuated tube[22]. It was a purple-brown crystalline solid which had to be handled either under nitrogen or in vacuum since it was unstable to air and hydroxylic solvents.

3.2 Electronic structure and spectroscopic properties of [3.3.3]cyclazine.

[3.3.3]Cyclazines may be discussed theoretically in terms of a linear combination of atomic orbitals (L.C.A.O.) approach. Qualitatively, it is useful to compare the cyclazine with the isoelectronic phenalenyl ring system (51).

The phenalenyl π-system has a non-bonding molecular orbital (N.B.M.O.) (52) which may be doubly occupied, singly occupied or unoccupied, thus giving rise to an anion, a free radical and a cation, all of which are stable. Replacement of the central C atom by N gives



(51)

(52)

[3.3.3]cyclazine (3), its radical cation and its dication, respectively. The [3.3.3]cyclazine radical cation and dication may be prepared by sequential oxidation of the parent [3.3.3]cyclazine with chlorine or bromine[22]. This facile oxidation is not unexpected, since U.V.P.E. spectroscopy[25a] shows that the first ionisation potential of (3) is unusually low, at 5.9 eV.

A comparison of the proton n.m.r. spectra of the diamagnetic members of the above series gives rise to some interesting results (Fig. 2). From structure (52) the atomic orbital coefficients of the N.B.M.O. are non-zero only at the α-positions. Thus the charge in the phenalenyl anion and cation must be largely concentrated at these positions. The effect on the α-proton signal (doublet) in the n.m.r. spectrum is seen as a shielding in the anion (53) and a deshielding in the cation (54), relative to the β-protons (triplet). The same effect is seen in the spectra of [3.3.3]cyclazine and its dication.

The overall effect of replacing the central carbon atom by nitrogen is to increase the positive charge by one unit, and thus the spectrum of the cyclazine dication (55)

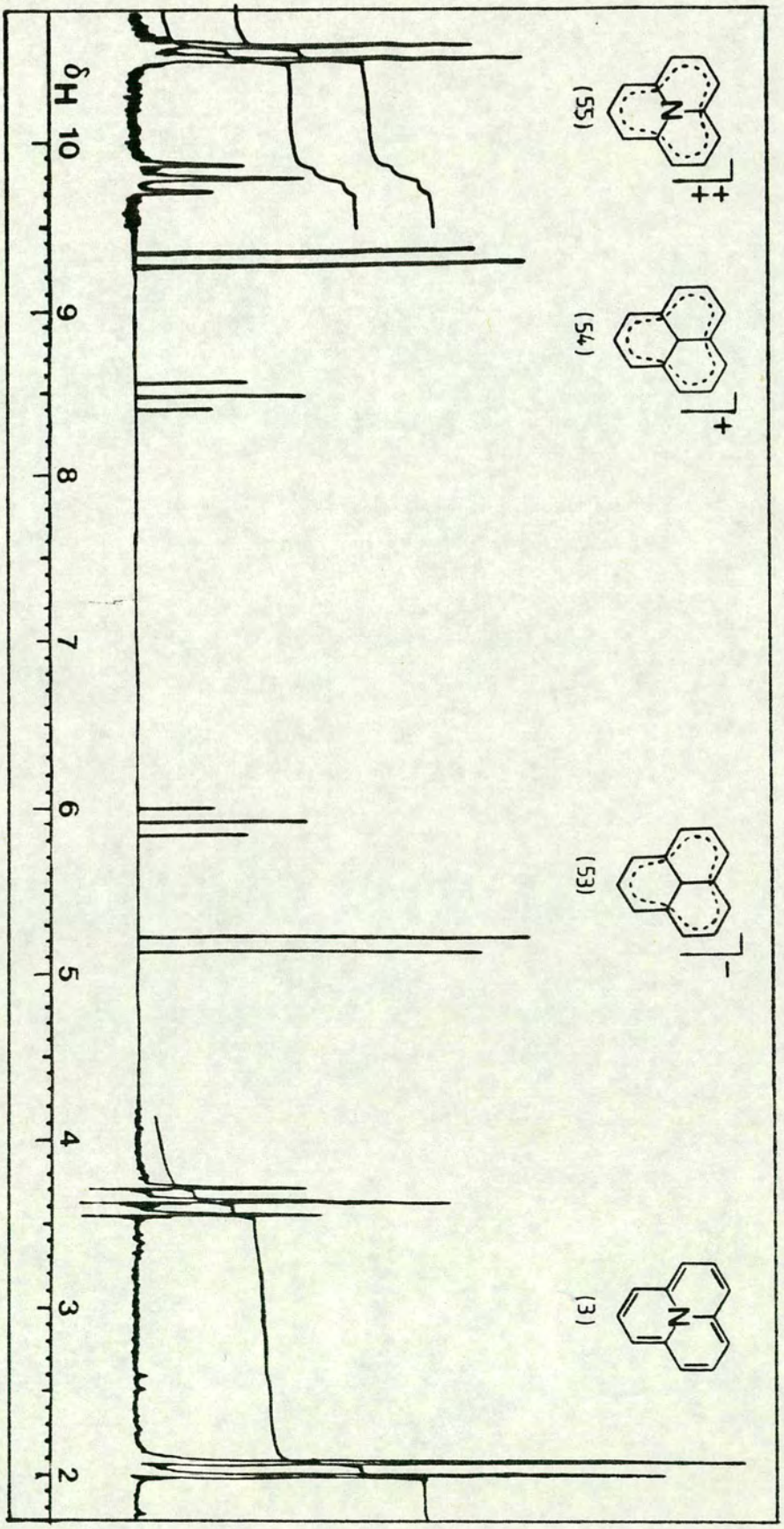
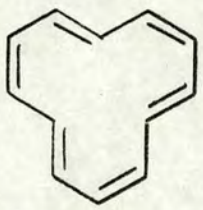


Fig. 2.

is shifted to a higher frequency relative to that of the phenalenyl cation. However, in going from the phenalenyl anion (53) to the neutral cyclazine (3), a shift to lower frequency is observed. This apparently anomalous result can be rationalised in terms of electron distribution, since the cyclazine would exist as a zwitterion if it were to retain the electron distribution of (53). In order to avoid this energetically unfavourable charge separation, the non-bonding electrons of the nitrogen atom tend to localise as a lone pair orbital, leaving a 12π-peripheral system equivalent to [12]-annulene (56). This



(56)

annulene perimeter sustains a paramagnetic ring current[22], which results in the protons of the parent [3.3.3]cyclazine being unusually strongly shielded at δ2.05 (α-protons) and δ3.58 (β-protons)[C_6D_6][26]. The ^{13}C n.m.r. spectrum[27a] shows no evidence of unusually high electron-density [δ164.3 (bridgehead-C), 141.1 (C-2), 107.3 p.p.m. (C-1)/ C_6D_6].

The above picture of a [12]annulene periphery predicts that [3.3.3]cyclazine should be antiaromatic and probably exists with alternating bond lengths[27]. The observation

of strong paratropism also indicates the existence of a low-lying excited electronic state which correlates well with the literature findings[27], as the first electronic transition occurs in the near infrared with unusually low energy (1290 nm; 93 $kJmol^{-1}$).

Molecular orbital calculations[25,26,27] also help to explain the chemistry of the [3.3.3]cyclazine system. A simple interaction diagram yielding the frontier orbitals of [3.3.3]cyclazine is obtained by a linear combination of the non-bonding M.O.'s of [12]annulene (56) and the nitrogen lone pair orbital (Fig. 3). This shows that the formal degeneracy of the non-bonding orbitals of (56) is lifted by interaction with the central nitrogen atom. The resulting frontier orbitals are close in energy, but are well separated spatially. The small H.O.M.O./L.U.M.O. gap arises due to the large energy difference between the interacting orbitals. This explains the susceptibility of [3.3.3]cyclazine to oxidation and reduction[22,25].

It may also be concluded from the interaction scheme that the properties of [3.3.3]cyclazines are very sensitive to inductive perturbations[27,28]. Thus the introduction of electron withdrawing groups (E.W.G.) or aza-substitution (eg. (57)) at the active ring positions C-1,3,4,6,7 and/or 9 has the effect of lowering the energy of the H.O.M.O. whilst leaving that of the L.U.M.O. unchanged. Thus, such a substitution confers extra stability on the [3.3.3]cyclazine nucleus, since the H.O.M.O.-L.U.M.O.

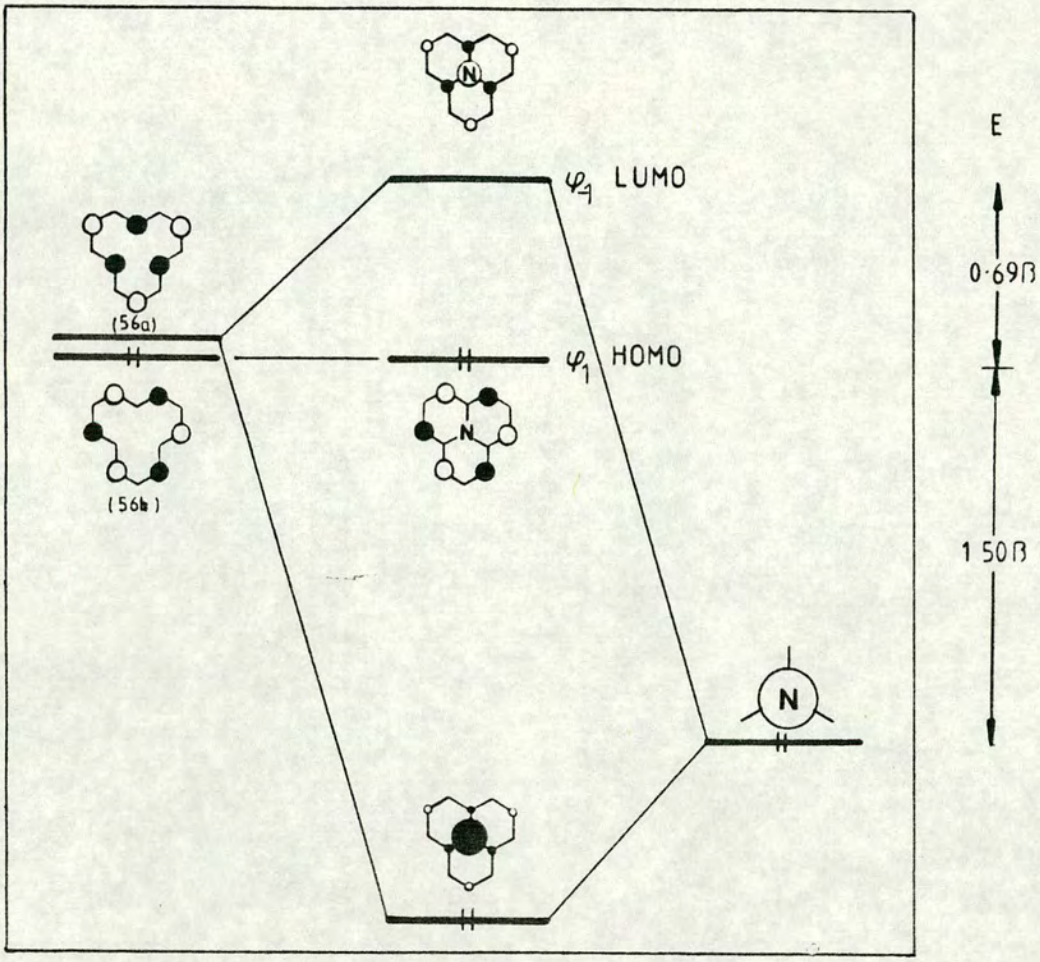
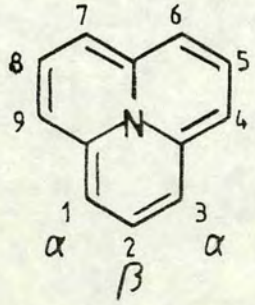
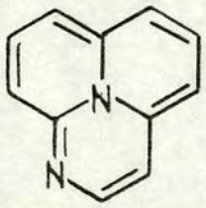


Fig. 3. (Not to scale)

energy gap increases. Several polyaza[3.3.3]cyclazine derivatives are known[5,29,30], and have also been studied (see also section 3.4). In n.m.r. spectra, electron withdrawing groups or nitrogen atoms in the α-positions have the expected deshielding effects[5,22], with a gradual change from paratropicity to diatropicity with increasing number of substituents. Electron withdrawing perturbations in the β-positions (C-2,5 and 8) of the [3.3.3]cyclazine skeleton (3) would be expected to exhibit the opposite effect i.e. the H.O.M.O.-L.U.M.O. gap would be decreased and the molecule would become less stable. Thus, it is not totally surprising that the synthesis of the latter type of substituted cyclazines remains a challenge.



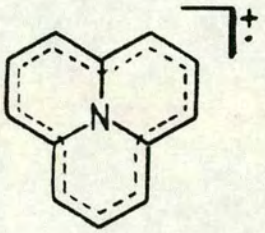
(3)



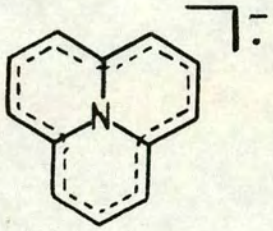
(57)

Electron spin resonance (E.S.R.) spectroscopy of the [3.3.3]cyclazine radical cation (58) ($a_{\alpha H}$, (-)6.45; $a_{\beta H}$, (+)1.78; a_N, (+)1.29 mT) has shown that the unpaired electron retains approximately the same distribution as in the phenalenyl radical[28c] ($a_{\alpha H}$, -6.29; $a_{\beta H}$, +1.81 mT), being concentrated at the α-positions. Conversely, the spin density in the radical anion (59) is largest at the

β-positions and at N($a_{\alpha H}$,(+)0.05; $a_{\beta H}$,(-)4.84; a_N,(+)6.54 mT) in conformity with the form of the L.U.M.O..



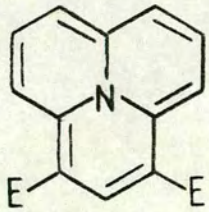
(58)



(59)

3.3 Reactions of [3.3.3]cyclazines

The instability of the parent [3.3.3]cyclazine[22] (3) has meant that not much chemistry has actually been done on the parent ring system. Instead, most of the investigations of reactivity have been carried out with the 1,3-di(ethoxycarbonyl)-derivative (47a), in which electron withdrawing substituents are present to stabilise the [3.3.3]cyclazine skeleton.



(47a)

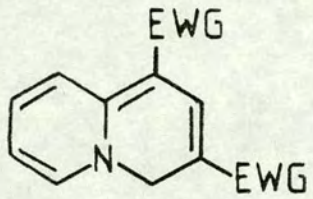
E = CO_2Et

The chemical reactivity of the [3.3.3]cyclazines reflects the lack of aromatic character, particularly in

the ease with which addition and oxidation reactions occur. The literature[12] also describes the fact that [3.3.3]-cyclazines undergo substitution reactions with electrophilic reagents, a type of reactivity commonly associated with aromaticity but also observed in many non-aromatic systems such as enamines.

3.3.1 Addition reactions (scheme 10)

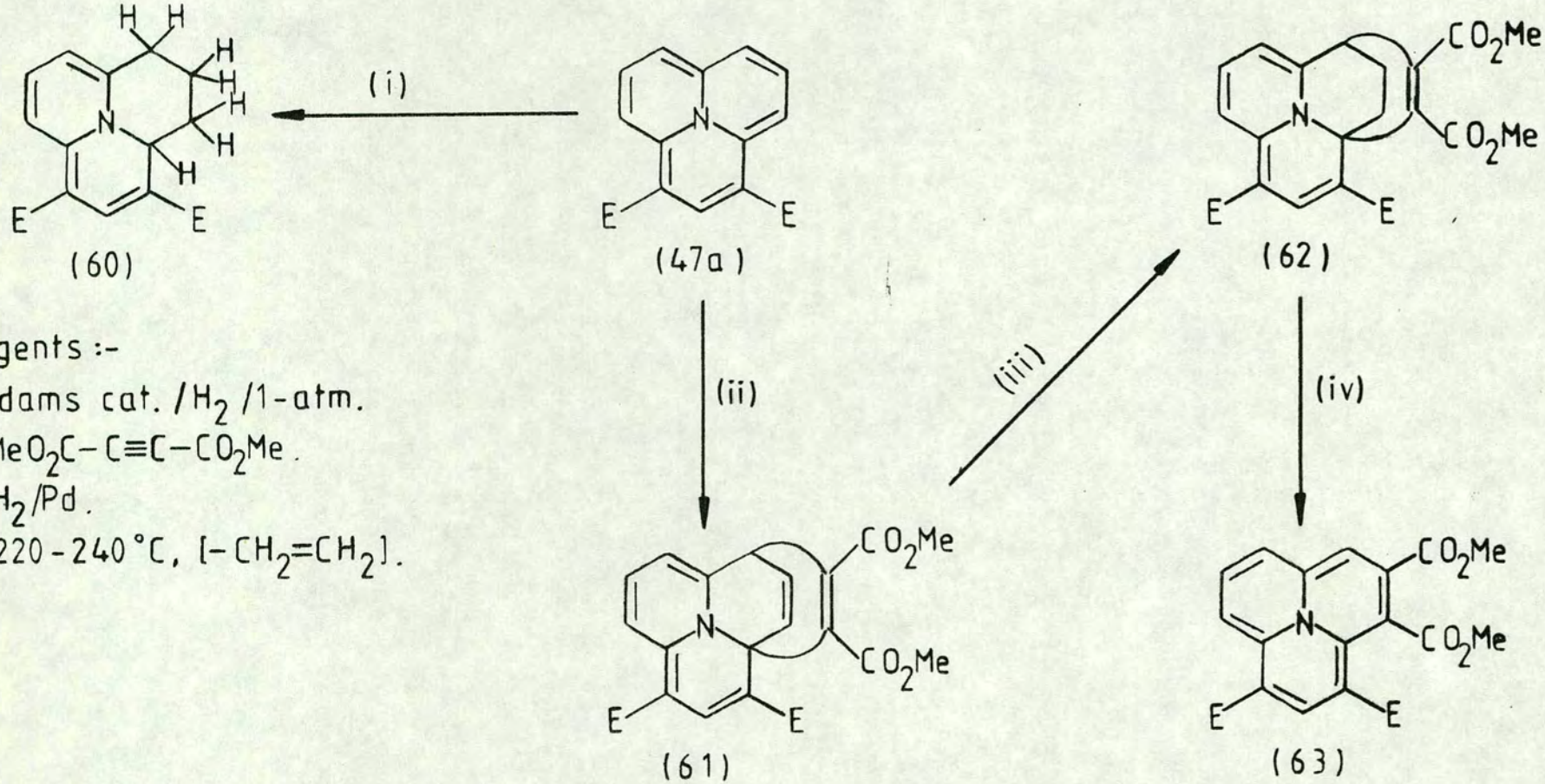
These in general proceed in such a manner that the residual conjugation of the adduct is present as a 4H-quinolizine substructure (50), bearing electron withdrawing groups at the C-1 and C-3 positions. This type of structure has already been noted in Leaver's synthetic



(50)

route to [3.3.3]cyclazines[22], and is recognisable in the Diels-Alder adducts and hydrogenation products by their red colour and characteristic u.v.-visible spectra.

A retro-Diels-Alder reaction regenerating the cyclazine structure is easily carried out after hydrogenation of the unconjugated double bond in the adduct (61).



Reagents :-

(i) Adams cat. / H_2 /1-atm.

(ii) $MeO_2C-C\equiv C-CO_2Me$.

(iii) H_2/Pd.

(iv) 220 - 240 °C, [$-CH_2=CH_2$].

Scheme 10.

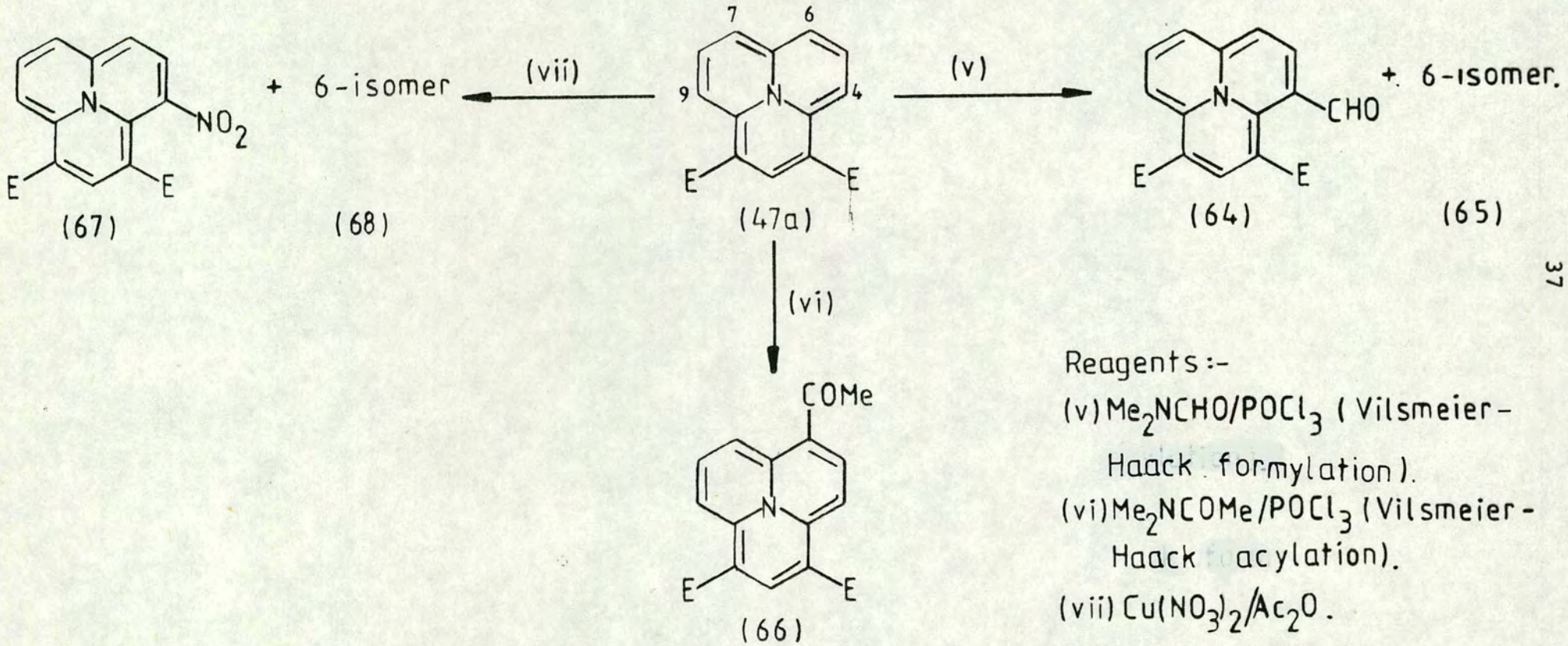
3.3.2 Substitution reactions (scheme 11)

Electrophilic substitution in [3.3.3]cyclazines has been observed[22] only in cases where one or more electronegative substituents are already present. In the diester (47), Vilsmeier acylation, nitration, and the Mannich reaction occur at one or more of the remaining α-positions, a mixture of 4- and 6- monosubstituted products being commonly observed. Such reactions at the C-4 and/or C-6 positions are as expected from consideration of the positions of maximum electron density around the periphery of the [3.3.3]cyclazine ring system (scheme 11).

3.3.3 Oxidation reactions

The only characterisable products obtained from the parent [3.3.3]cyclazine (3) were formed in reactions with electron-transfer oxidants. The first product of such oxidation reactions is the cyclazine radical cation which was shown by e.s.r. spectroscopy[22], to be present in the blue solution obtained by treating the cyclazine with silver(I) perchlorate in acetonitrile. By using bromine vapour as the oxidant, the radical cation bromide (72) can be isolated as a stable blue solid which is further oxidised with an excess of bromine vapour, to the greenish-brown dication dibromide (73) (scheme 12).

Similar oxidations of the 1,3-disubstituted-[3.3.3]-cyclazine (47a) did not give stable monomeric cations, though blue intermediates, presumably radical-cation salts, were often observed. After disappearance of the blue colour, dimeric products were isolated in the form of the



Scheme 11.

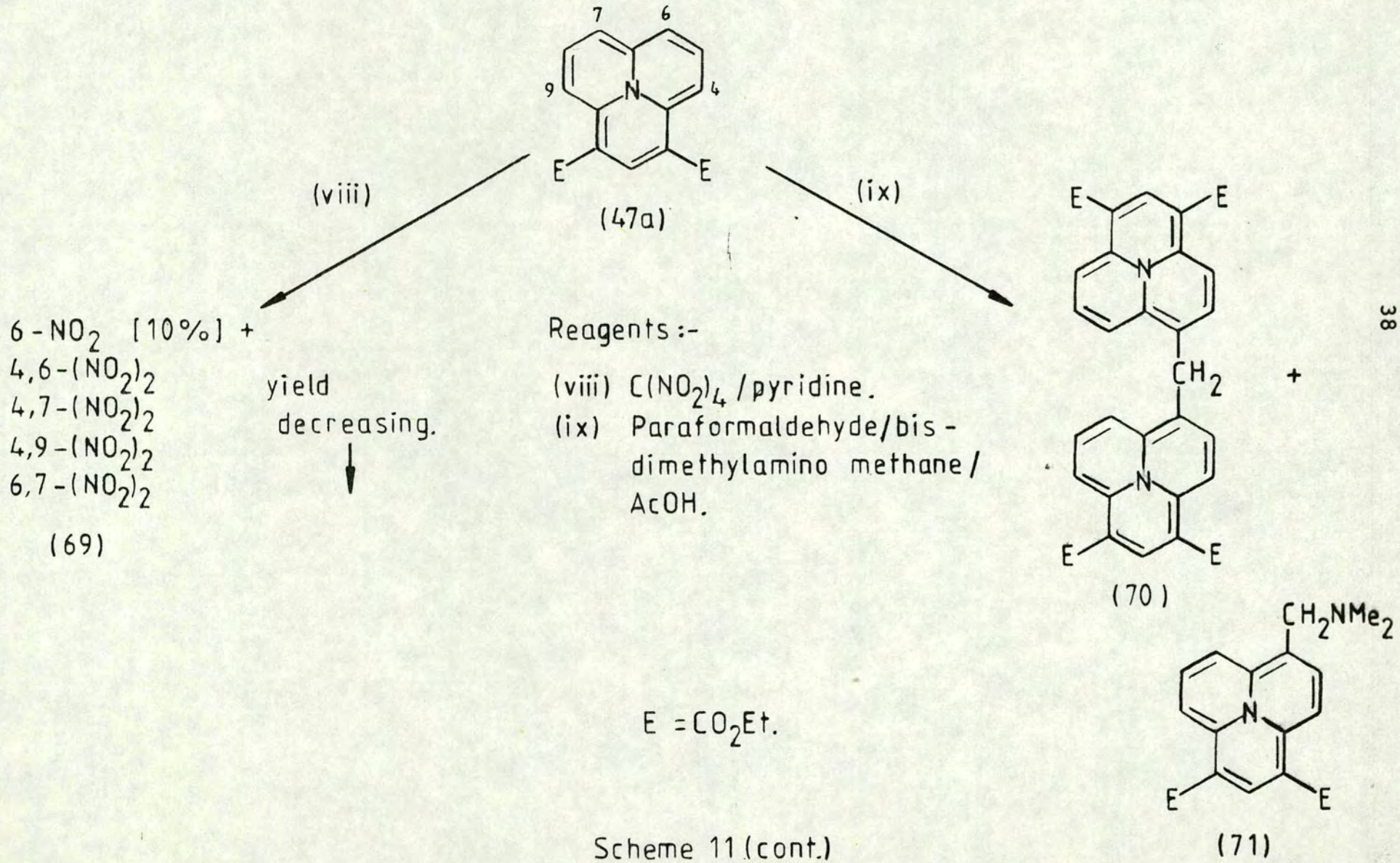
Reagents:-

(v) $Me_2NCHO/POCl_3$ (Vilsmeier-Haack formylation).

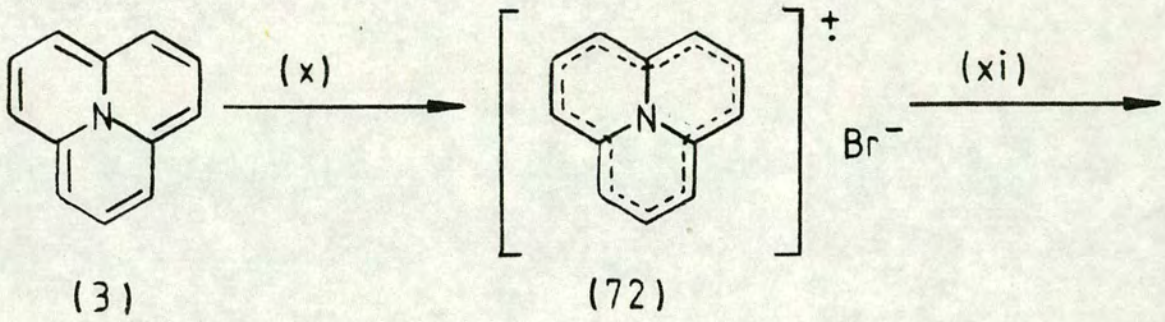
(vi) $Me_2NCOMe/POCl_3$ (Vilsmeier-Haack acylation).

(vii) $Cu(NO_3)_2/Ac_2O$.

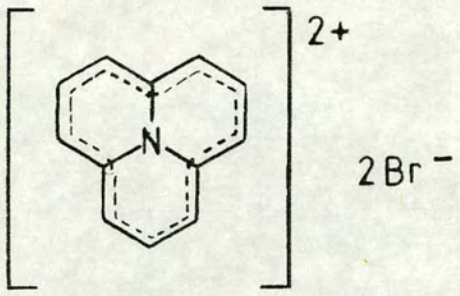
cont.



Scheme 11 (cont.)



(3) (72)



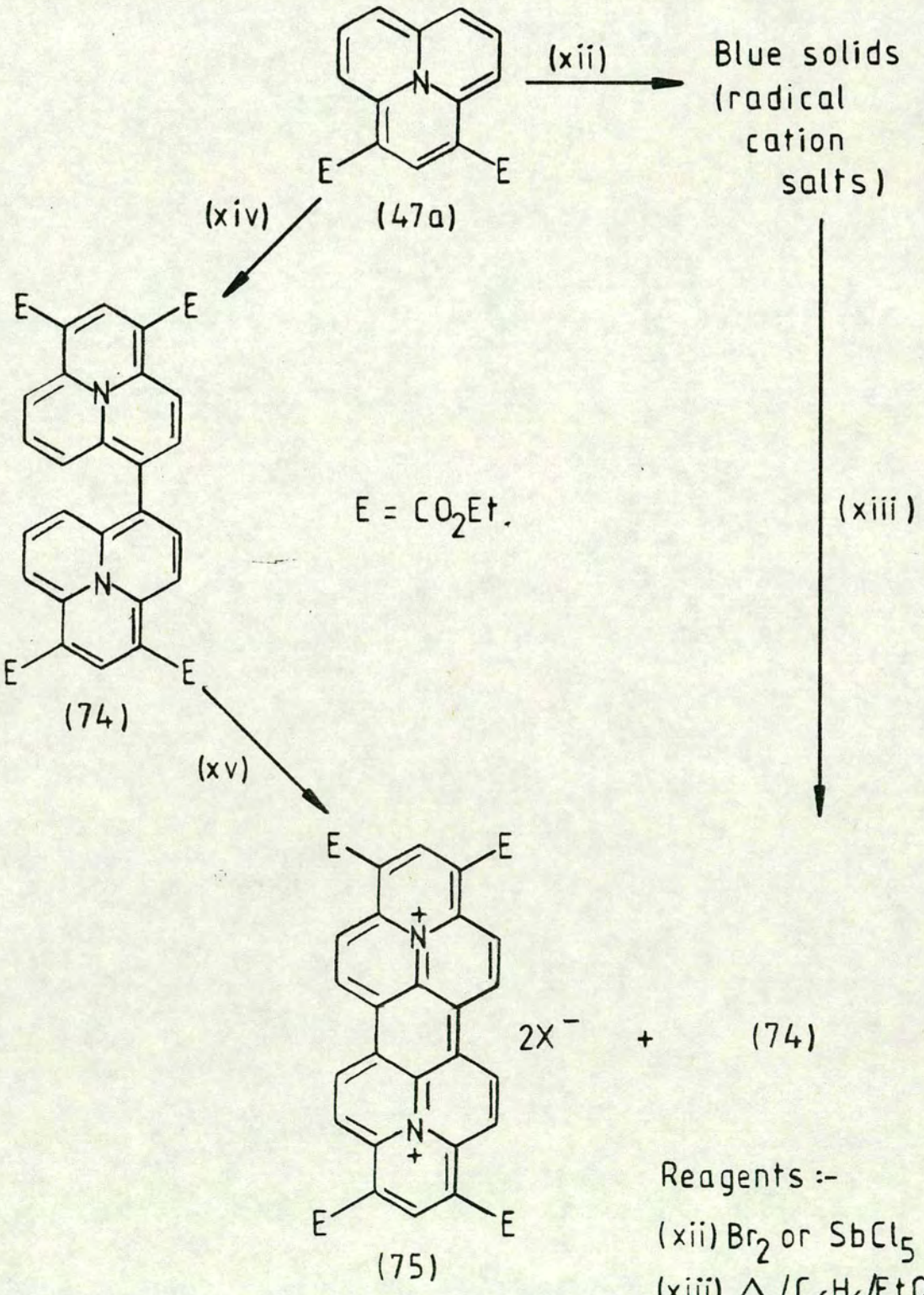
(73)

Reagents:-

(x) Br_2 vapour.

(xi) Excess Br_2 vapour.

Scheme 12.



Reagents :-

(xii) Br_2 or $SbCl_5$.

(xiii) Δ / C_6H_6/EtOH.

(xiv) NBS/CH_2Cl_2/-78°C

(xv).a) Br_2/C_6H_6.

b) EtOH.

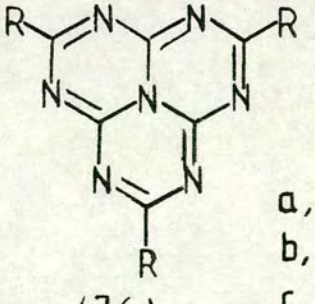
Scheme 13.

bicyclazine (74) and/or the diazoniadibenzoperylene salt (75) (scheme 13).

3.4 Preparation of [3.3.3]cyclazines from aza[3.3.3]cyclazines

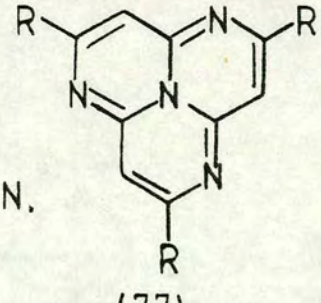
The existence of aza[3.3.3]cyclazines goes back to the nineteenth century, when in 1835, Gmelin described[31] an undesirable by-product, tripotassium melonate (76a) obtained when sulphur, potassium ferricyanide and potassium carbonate were heated together during the preparation of potassium thiocyanate. These heat stable, insoluble, chemically active compounds with a $C_6H_7N_7$ nucleus were known as melon and melem derivatives.

Almost a century later, Pauling and Sturdivant[32a] established the structure of the Gmelin's by-product by physical methods, and described it as a coplanar arrangement of three fused s-triazine rings as represented by structure (76). Synthesis of other derivatives (76b-d) have also been reported[32b].



(76)

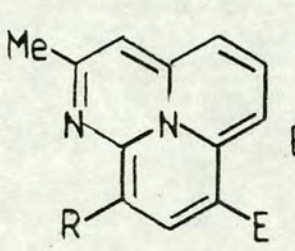
a, R=N(K)CN.
b, R=Cl.
c, R=OK.
d, R=OH.



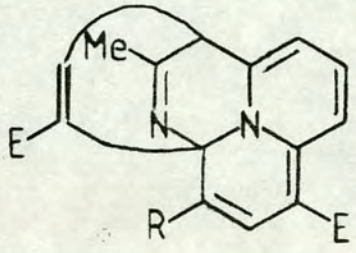
(77)

A triaza[3.3.3]cyclazine (77) was reported in the thesis of Mrazek[33a] as early as 1946. The 1,4,7-triaza-derivative was also noted by Van Winkle[33b] in the 1960's although it was never fully characterised. More recently, systematic studies of aza[3.3.3]cyclazines have been carried out by several research groups, and this work has been included in reviews[4,5].

From the viewpoint of the present work, the one aspect of azacyclazine reactivity that seems worthy of mention is their transformation into [3.3.3]cyclazines by cycloaddition followed by retro-cycloaddition. For example, the compounds (78), when treated with methyl propiolate as the dienophile, gave the substituted [3.3.3]cyclazines (80), with loss of acetonitrile[34].

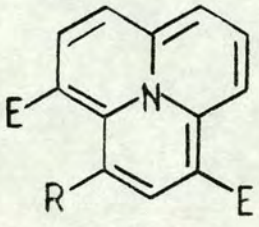


(78)



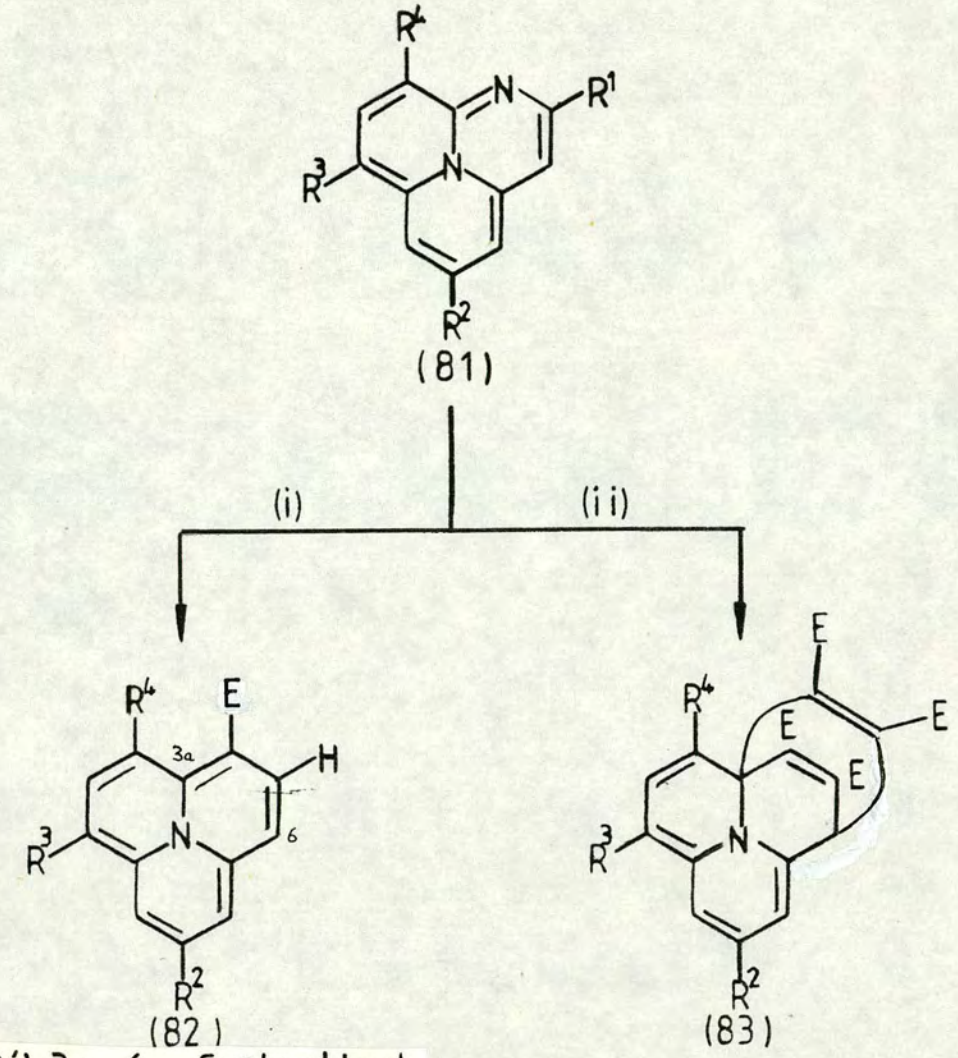
(79)

E=CO_2Me.
a, R=CN.
b, R=CO_2Et.



(80)

It is reasonable to suppose that the adducts (79) are intermediates in this transformation. A more recent example of the same retro Diels-Alder reaction using methyl propiolate and dimethyl acetylenedicarboxylate[35] gave substituted cyclazines (82) and products (83) of further cycloaddition as shown in scheme 14.



+ (82′) 3a, 6 – Cycloadduct.

	R^1	R^2	R^3	R^4
a.	H	H	CO_2Me	CN
b.	Me	H	"	"
c.	Me	Me	"	"

E = CO_2Me.

Reagents: (i) E–C≡C–H

(ii) 2E–C≡C–E.

Scheme 14.

SECTION II

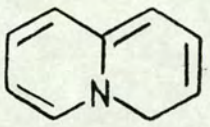
DISCUSSION

SECTION 2

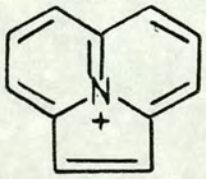
DISCUSSION

1. Aims of the project

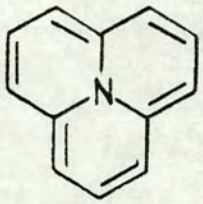
Most of the work contained in this thesis is concerned with cyclazines that contain a quinolizine moiety (84). As described in the introduction, [2.3.3]cyclazines (2) and [3.3.3]cyclazines (3) have been synthesised previously in these laboratories from quinolizine derivatives.



(84)



(2)



(3)

The first objective of this project was to develop a new synthetic method that would provide [3.3.3]cyclazines in better yield and by a smaller number of steps than the previous method[22]. It was desirable that the approach adopted should be applicable to synthesis of [3.3.3]cyclazines with a variety of substituents.

With such a method to hand, the second objective was to carry out futher investigations into the chemistry of [3.3.3]cyclazines. It was intended that some of this work would involve extensions of previously discovered reactions and that some would be a search for new reactions. Two of the desirable targets in this area would be (a) a method

for annelation of [3.3.3]cyclazines that could lead to benzo-derivatives, and (b) a method of ring expansion that would be capable of converting [3.3.3]cyclazines into the as yet unknown [3.4.4]cyclazines.

In addition, flash vacuum pyrolysis techniques were to be applied to a variety of quinolizine derivatives with a view to generating [2.3.3]- or [3.3.3]cyclazines by unusual cyclisation processes.

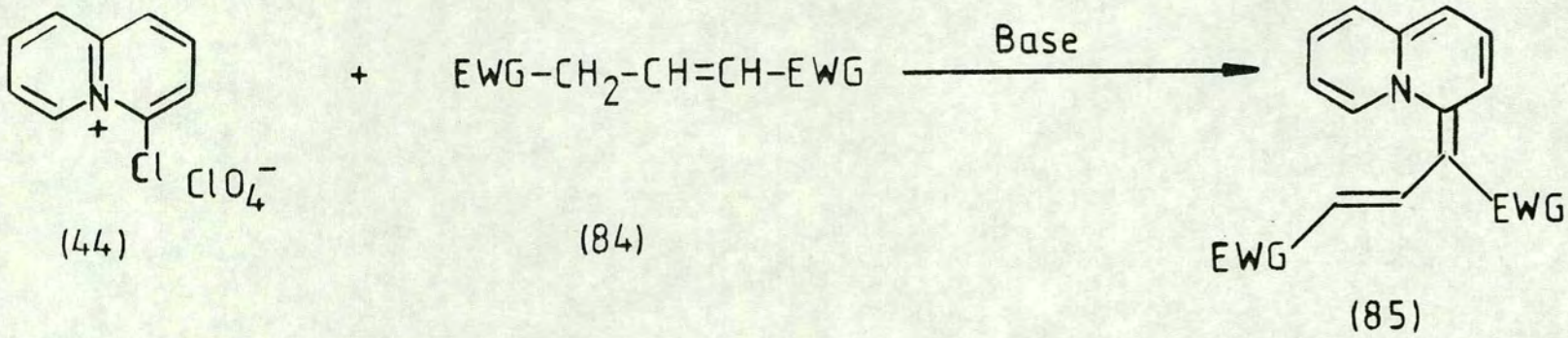
2. Investigation of a novel route to [3.3.3]cyclazine derivatives

2.1 Introduction

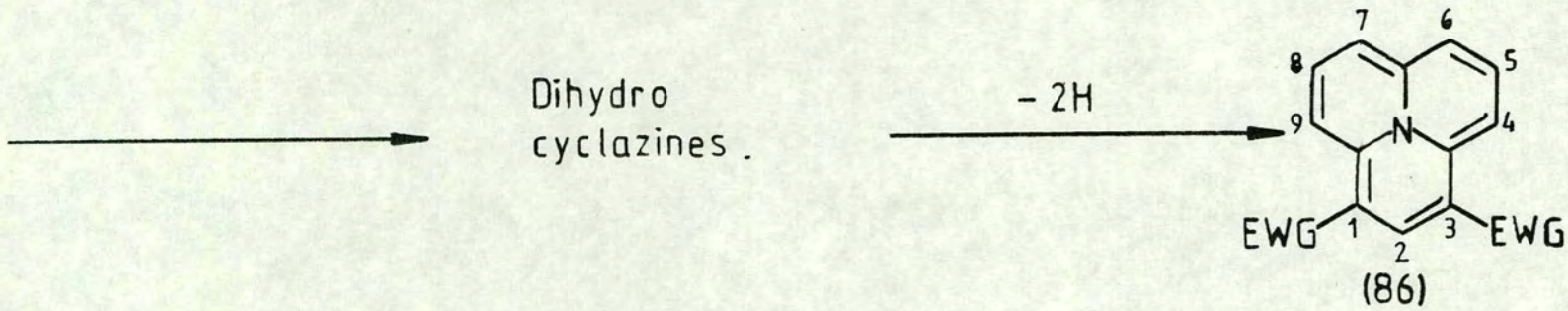
The previous route to [3.3.3]cyclazine has been discussed in the introduction (scheme 8).

In broad outline, this approach involved the construction of the twelve-carbon cyclazine skeleton from a nine-carbon component (quinolizine), a one-carbon component (reactive methylene compound), and a two-carbon component (acetylene). It suffered from the disadvantage that the intermediate ten-carbon compounds (quinolizin-4-ylideneacetates) (46) were difficult to handle, because of their sensitivity to air.

The new approach[36] (scheme 15) was to utilise the 4-chloroquinolizinylium ion (44) as a nine-carbon component, which would be condensed with a three carbon component in the form of a reactive propene derivative (84). At the outset, therefore, the number of components would be

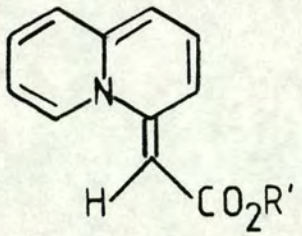


(44) (84) (85)



(86)

Scheme 15 .



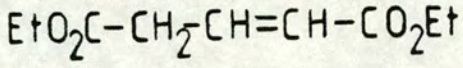
(46)

a: R' = Et

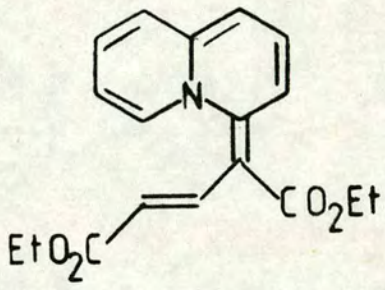
b: R = Bu^t

reduced from three to two and the expected intermediate (85) would be stabilised by the presence of two electron-withdrawing groups, both of which are in conjugation with the N lone-pair of the quinolizine ring. It was envisaged that these two groups would be retained in the second stage, thus providing stabilisation of the cyclazine product, as in the previous synthesis. Among the problems that might be encountered would be (a) the possible existence of structure (85) in a stereoisomeric form, unfavourable for cyclisation and/or (b) failure to find a method that would cyclise (85) to generate the tricyclic structure (86) desired.

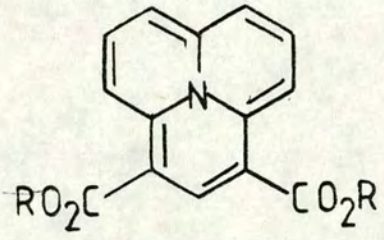
At the time the present work was started, some preliminary work on scheme 16 had been carried out by McGuire[37] who had used diethyl glutaconate (87) as the propene and sodium hydride as the base. The quinolizinylideneglutaconate (88) was not observed in this reaction but, unexpectedly, the [3.3.3]cyclazine (47) was formed directly in low yield, and an impure specimen of its



(87)



(88)



(47)

a: R = Et.

3a,4-dihydro derivative (49) was isolated from the same reaction mixture by preparative thin layer chromatography. Other products, including an unstable orange compound and a red baseline material were noted on t.l.c., but not characterised. Formation of the 3a,4-dihydro derivative indicated some relationship to the previous route[22], and was encouraging since it was known that this compound could be dehydrogenated to the cyclazine (47). Based on this initial groundwork, suggesting that the new approach was viable, an optimised procedure was sought that would improve on the yield[22] (46%) of the diethyl ester (47a) obtained by the previous three-stage route.

2.2 Reaction of 4-chloroquinolizinylium perchlorate with diethyl glutaconate: A new route to dihydro-[3.3.3]cyclazines

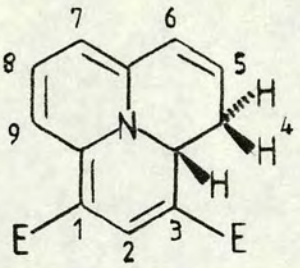
2.2.1 Identification of the products

Following the method developed earlier[22] for the preparation of quinolizinylidenemalonates, the initial synthetic approaches started with the generation of the diethyl glutaconate anion (87^-) in THF at room temperature using sodium hydride as the base. The 4-chloroquinolizinylium perchlorate salt (44) was added at 0°C in small aliquots and the reaction mixture was allowed to come to room temperature. Some interesting colour changes took place as the reaction proceeded. The initial clear yellow colour of the diethyl glutaconate ion (87^-) in solution gave way to an orange-red colour on addition of the perchlorate salt. On warming to room temperature, the stirred mixture gradually darkened to a purple colour, which is characteristic of the 3a,4-dihydrocyclazine derivative. Analytical t.l.c. (silica and alumina) showed orange and purple spots of similar Rf values, and later a yellow spot appeared corresponding to the fully unsaturated [3.3.3]cyclazine (47a). The purple spot was shown to be the 3a,4-dihydro derivative by t.l.c. comparison with an authentic sample.

As mentioned earlier, these experiments gave rise to the 3a,4-dihydrocyclazine and to a trace of the fully unsaturated [3.3.3]cyclazine diester without any deliberate

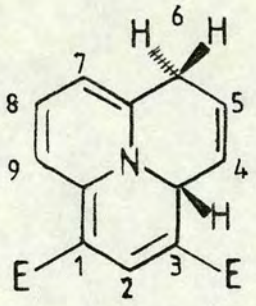
dehydrogenation step. Two other products were also noted by McGuire[37], but were not identified. In the present work, it proved possible, by careful chromatographic work-up, to obtain these materials in a sufficiently pure state for investigation by proton n.m.r., and other spectroscopic techniques.

The unstable orange material, which had an Rf value just slightly less than that of the 3a,4-dihydro compound on t.l.c., was obtained by medium pressure liquid chromatography (M.P.L.C.) and identified as the 3a,6-dihydro[3.3.3]cyclazine (89) largely on the basis of its ^{1}H n.m.r. spectrum, which was obtained immediately after isolation of the compound. The presence of a 4H-quinolizine substructure was clearly apparent from a comparison with the spectrum of the 3a,4-dihydro compound (49). Thus, the signals due to H-2,7,8 and 9 showed



(49)

E = CO_2Et.



(89)

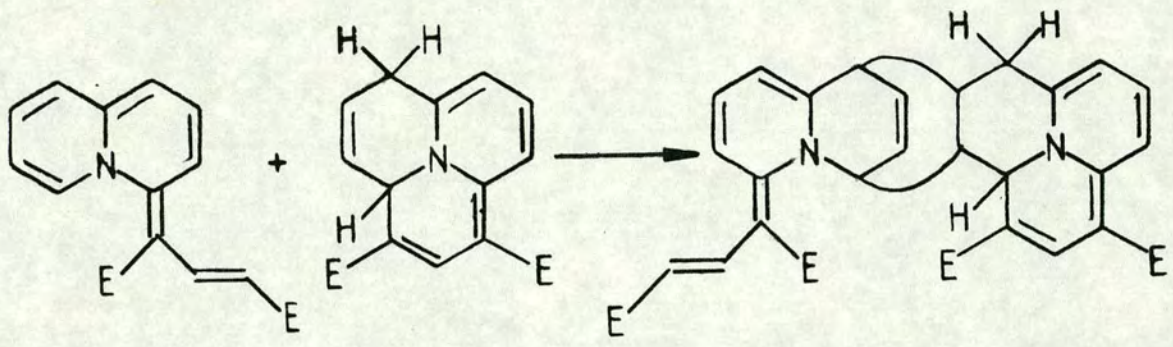
similar chemical shifts and coupling constants in both isomers (Tables 1, 2; experimental section). A crucial feature in the identification of compound (89) was the small triplet splitting (^{4}J, 0.9Hz) of H-7 caused by the CH_2 protons which must therefore be present at C-6.

The complex spin system in the partially saturated ring was sufficiently well resolved at 200 MHz, for accurate assignments to be made, and these again supported the 3a,6-dihydro structure. Details of the spectrum are tabulated in the experimental section, along with the corresponding ^{1}H and ^{13}C n.m.r. data for (49) (Table 2A).

The 3a,6-dihydro isomer (89) could not be characterised completely because of its tendency to spontaneously convert partially into the 3a,4-dihydro isomer (49) and partially into the fully unsaturated cyclazine (47a). It was therefore not obtained in analytically pure form.

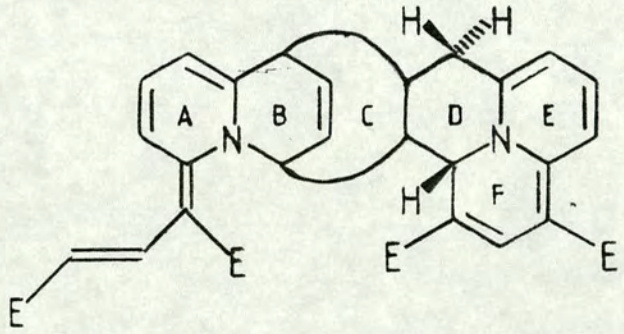
The other previously unidentified product was a slightly unstable red solid of relatively high melting point (201-204°C) and low chromatographic mobility. Its mass spectrum showed a peak at m|z 626, attributed to the molecular ion, which corresponds formally to a dimer of a dihydrocyclazine. Although the compound could not be conclusively identified, it was possible to interpret its n.m.r. spectrum in terms of a structure such as (91) which is a Diels-Alder adduct derived from a quinolizinylidene-glutaconate (90), acting as a diene, and a dihydrocyclazine (89), acting as a dienophile.

The salient features of the spectrum (see experimental section for tabulated details - Table 3) were (i) a series of four one-proton signals, identifiable from their chemical shifts and multiplicities as being due to a 4H-quinolizine moiety (rings E and F) like that in the



(90) (89) (91)

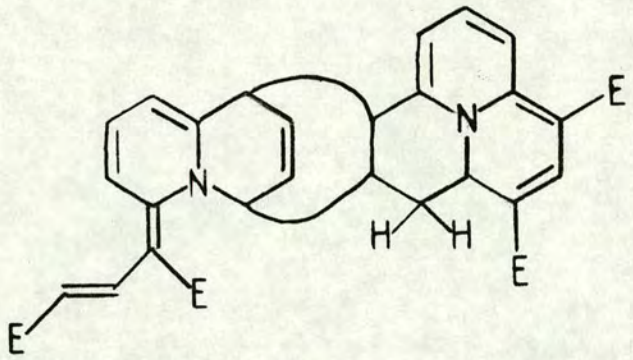
dihydrocyclazines (49) and (89), (ii) an AX system (J_{AX} 15.1 Hz) corresponding to the protons of a trans-1,2-disubstituted double bond (glutaconate side chain attached



(91)
E = CO_2Et.

to ring A), (iii) an AMX system attributable to the protons of ring A, and (iv) a complex spin system (9H) correlating well with the protons of rings B, C and D.

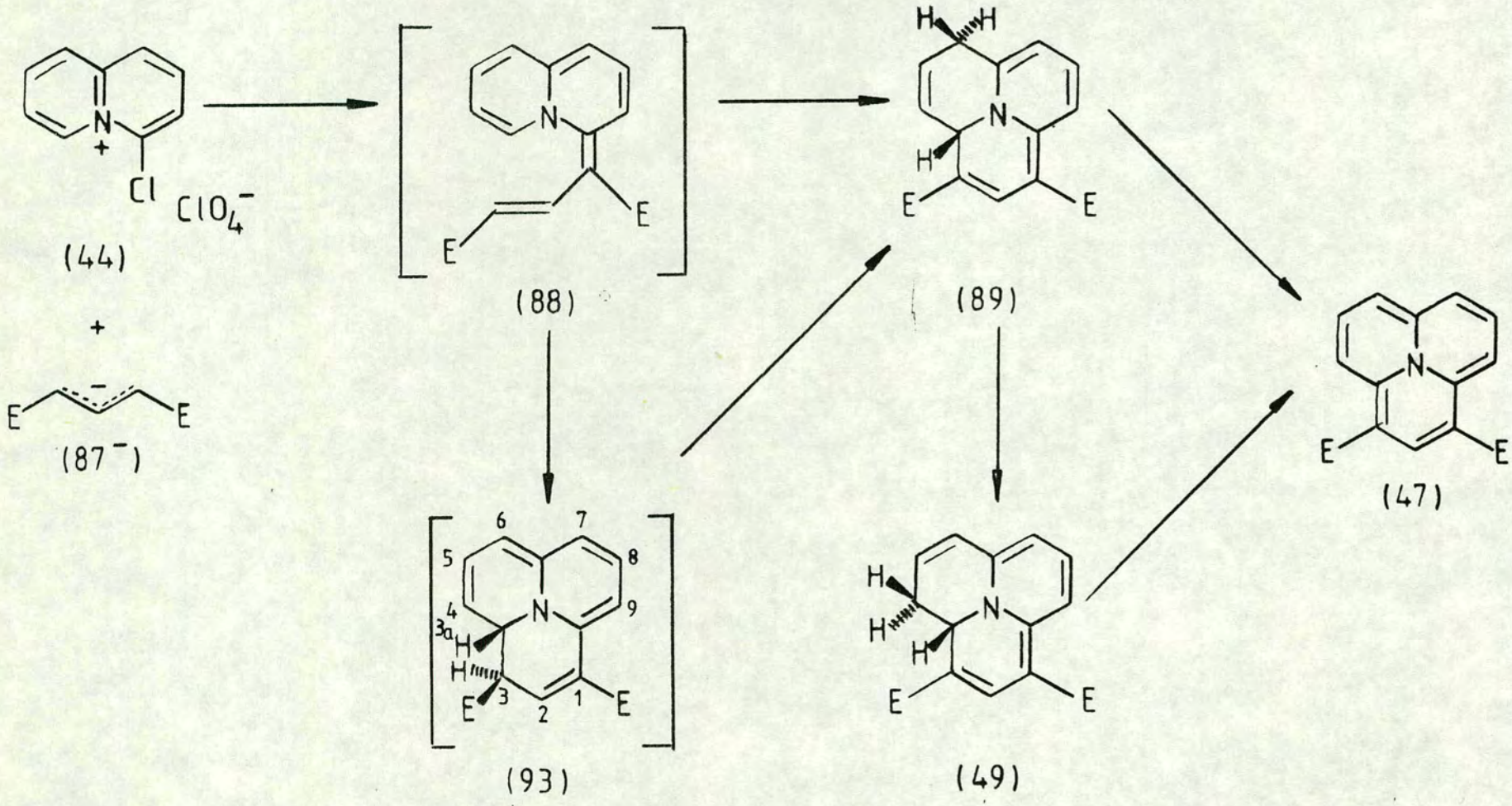
It should be noted that isomers of (91) can also be drawn that fit the n.m.r. picture equally well (eg. (92)). There is however, no precedent for dienophilic reactivity in dihydrocyclazines or of dienic reactivity in quinolizinylidene derivatives.



(92)

At temperatures of 180-200°C in the mass spectrometer, the dimer gave fragment ions at m|z = 313 and 311, which correspond to the dihydrocyclazine and the fully unsaturated cyclazine respectively, and which could have been formed by a retro-Diels-Alder reaction with partial dehydrogenation. Unfortunately, it was not possible to obtain a sufficient quantity of the pure dimer for further investigation. A ^{13}C n.m.r. spectrum would have been particularly valuable as supporting evidence for the central portion of the molecule.

A probable sequence of intermediates leading to the dihydrocyclazines (49) and (89) is outlined in the reaction scheme (scheme 16). By analogy with the corresponding malonate and cyanoacetate reactions, it is reasonable to assume that the glutaconate reacts with the quinolizinylium salt (44) to produce (88) as the first intermediate. The first observable intermediate appears to be the 3a,6-dihydro-[3.3.3]cyclazine derivative (89) but, since there is no obvious direct route from (88) to this compound, it is



Scheme 16.

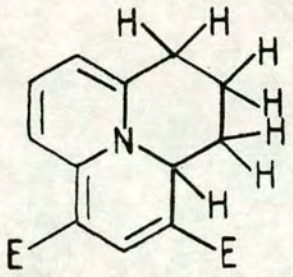
suggested that the initial cyclisation leads to a 3,3a-dihydrocyclazine (93) by a thermally allowed conrotatory electrocyclic process. The 3,3a-dihydrocyclazine which contains a 4H-quinolizine substructure with no electron withdrawing substituents, rearranges by hydrogen migration to the more stable 4H-quinolizine derivative (89). Although this migration is a [1,9]-shift and therefore allowed in a concerted suprafacial mode, it is likely that the rigidity of the ring system would render the transition state for concerted migration sterically inaccessible (ie. the two migration termini are too far apart). The migration is therefore thought to be prototropic and non-concerted, re-protonation at C-6 being kinetically preferred to reprotonation at C-4, because C-6 is sterically more accessible to an external proton donor.

The 3a,4-dihydrocyclazine (49) is presumably the thermodynamically-preferred product because of its more extensive conjugation. The spontaneous formation of the fully unsaturated cyclazine from the 3a,6-dihydro-compound but not (or only slowly) from its 3a,4- isomer is possibly due to the fact that a concerted 1,4- elimination of H_2 is thermally allowed whereas the corresponding 1,2-elimination is thermally forbidden.

2.2.2 Optimisation of yield

The identification of the major initial reaction products as dihydrocyclazines provided the basis for the use of u.v.-visible spectroscopy to estimate approximate yields before work up. The strongly-coloured solution

obtained after addition of the quinolizinylium salt had absorption maxima (at 505 and 365 nm) which are very close to those reported[22] for the 3a,4,5,6-tetrahydro [3.3.3]-cyclazine derivative (94) (507 and 362 nm).



(94)

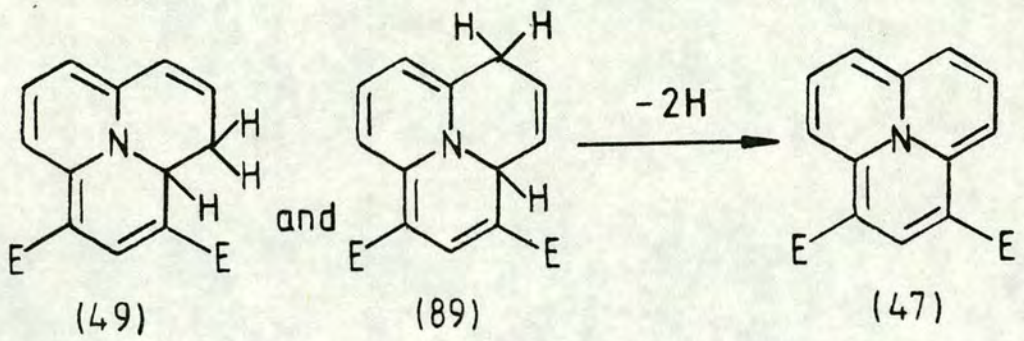
This result is consistent with the presence of the 3a,6-dihydrocyclazine (89) as the major isomer and, in conjunction with analytical t.l.c. observations, shows that this dihydro-isomer is the first one observable as the reaction proceeds. The corresponding absorption maxima for the more conjugated 3a,4-dihydro isomer (49) are at longer wavelengths (530 and 398 nm)[22]. Accordingly, absorbance measurements were made at 505 nm (after dilution of an aliquot of the reaction solution) and yields were calculated based on the assumption that the 3a,6-dihydro-compound would show essentially the same extinction coefficient for its long wavelength absorption maximum as does the tetrahydro-compound (94), a similar chromophore being present in both compounds.

The most significant improvement in yield, as shown by the u.v. experiments, was achieved by changing from sodium hydride to lithium diisopropylamide (LDA) as the

base for generation of the ester enolate. This base, generated *in situ*[38] at low temperatures, had the advantage of being soluble in tetrahydrofuran (THF). It reacted rapidly and completely with diethyl glutaconate at -78°C, thus preventing the Michael reaction of this α,β-unsaturated ester with its own anion. By maintaining the low temperature (-78°C) during initial reaction with the 4-chloroquinolizinylium salt (44), and by using more dilute solutions, the formation of by-products such as the red dimer was minimised and the yields of dihydrocyclazines were very much improved, as indicated by u.v. and t.l.c. analysis of reaction mixtures.

To summarise, a set of optimum conditions using LDA and low temperatures gave the dihydro cyclazines in yields of approximatley 50% when isolation was by column chromatography on neutral alumina. It is known that there are some losses of product during the column chromatography stage, as the adsorbent frequently exhibits irreversible staining. It was hoped, therefore, that chromatography at this stage could be avoided completely, and that a "one-pot" synthesis, incorporating the dehydrogenation step, might eventually be possible. The next task however, was to search for an efficient means of dehydrogenation of the dihydrocyclazines.

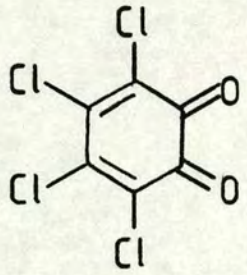
2.3 Dehydrogenation of the dihydro[3.3.3]cyclazines



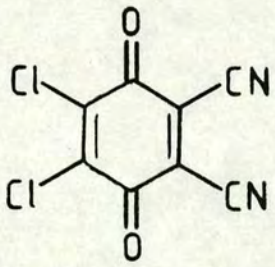
(49) (89) (47)

In the previous synthesis[22] of [3.3.3]cyclazines, cycloaddition and dehydrogenation were carried out in one operation by using boiling nitrobenzene as the solvent (scheme 8). It was noted in the present work, however, that dehydrogenation of isolated dihydro[3.3.3]cyclazines in nitrobenzene gave yields of fully unsaturated cyclazine as low as 2-20%. Extensive decomposition was obvious. A search was therefore initiated to find a dehydrogenating reagent that would be efficient at much lower temperatures than refluxing nitrobenzene (210°C).

Dehydrogenation of hydroaromatic substrates[39] is commonly carried out at moderate temperatures (80-120°C) with various high potential quinones[40], among which ortho- and para-chloranils (tetrachlorobenzoquinones) (eg. 95) and DDQ (2,3-dichloro-5,6-dicyano-para benzoquinone) (96) are the best known examples. However, when used here, these quinones gave only very small amounts of the fully unsaturated cyclazine despite the mild conditions employed



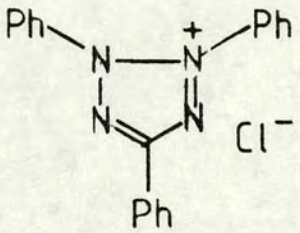
(95)



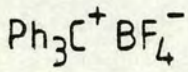
(96)

(eg. THF/room temperature). Further investigation revealed that these quinones reacted with the cyclazine itself once formed, giving decomposition products. In retrospect, the known susceptibility[22] of the [3.3.3]-cyclazine to electron-abstraction is probably a major factor here, the quinones being powerful electron-acceptors.

Other dehydrogenating reagents such as 2,3,5-triphenyl-tetrazolium chloride (T.T.C.)[41] (97) and trityl fluoro-borate[42] (98) have the disadvantage of producing acidic by-products (HCl and HBF_4) which could cause decomposition of the cyclazine. When a small excess of the former reagent



(97)



(98)

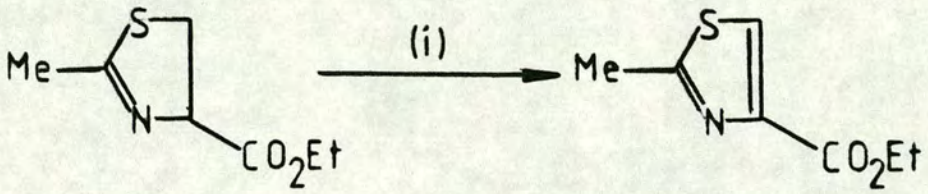
was refluxed in pyridine with the 3a,4-dihydro cyclazine, in the presence of various acid scavengers (anhydrous K_2CO_3 or molecular sieve 5A), only a 50% yield of dehydrogenated product could be obtained. Trityl fluoroborate, under similar conditions gave only decomposition

products and a small amount of recoverable dihydro compound.

Manganese dioxide, another reagent which has been used in dehydrogenations, reacted with the 3a,4-dihydro-[3.3.3]cyclazine (49) to give only a trace of the fully unsaturated cyclazine after 72 hours stirring at room temperature in acetonitrile. T.l.c. provided evidence for the formation of some 6,6'-bicyclazinyl compound (74), as has been observed in previous oxidation reactions[22].

Palladium-charcoal (Pd/C) and nickel peroxide when tested[43] with the 3a,4-dihydro[3.3.3]cyclazine (49) in various low boiling solvents (THF , CH_2Cl_2) did not give the cyclazine, but instead gave products of low chromatographic mobility, visible as a yellow and a pink spot on t.l.c.. These products were also formed when a small amount of the cyclazine itself was tested under identical conditions, thus indicating that these products are probably formed by further oxidation of the dehydrogenated product.

The possibility of the cyclazine itself being further oxidised, following dehydrogenation, suggested that 9,10-phenanthraquinone (101), which has a lower oxidation potential than the chloranils and DDQ, might be a more satisfactory dehydrogenating reagent. 9,10-Phenathraquinone has been previously reported[44] as being a suitable dehydrogenating reagent for the quantitative conversion of thiazolines (99) into thiazoles (100) (scheme 17). The higher potential quinones were described as unsuitable for this latter dehydrogenation also.

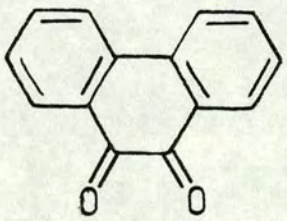


(99) (100)

Reagents :-

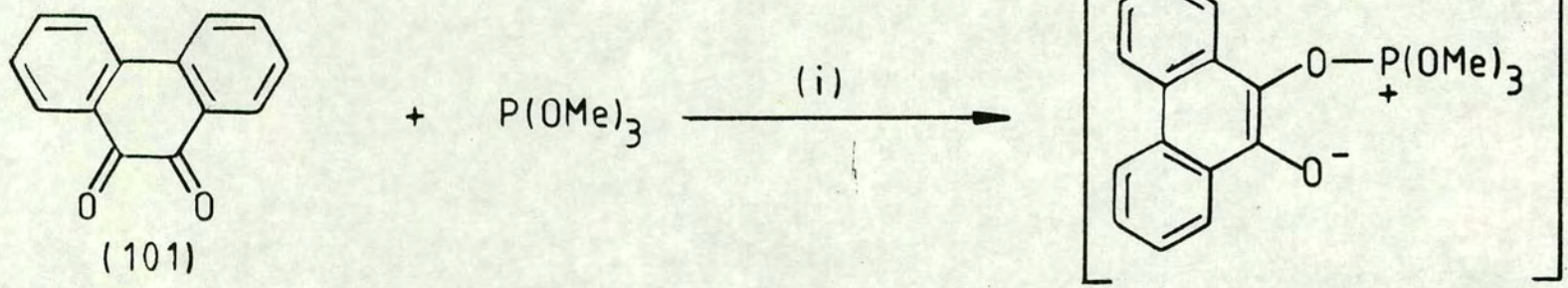
(i) 9,10-Phenanthraquinone (101) / AcOH / - 0·5h / 100%.

Scheme 17 .



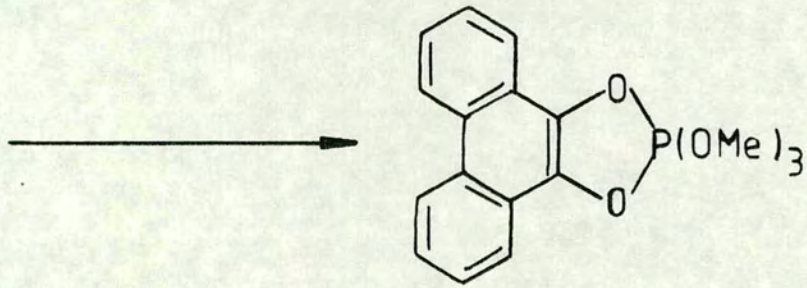
(101)

Initial small scale tests using (101) in refluxing THF showed a smooth dehydrogenation of the 3a,4-dihydro compound to its fully unsaturated derivative. Further investigation showed that the cyclazine (47) could be obtained in overall yields of 50-60% from the chloroquinolizinylium salt (44) by isolation of the intermediate dihydrocompounds and treatment with a small excess of phenanthraquinone. It was observed, however, that the cyclazine (47a) and phenanthraquinone are very similar in solubility and in chromatographic behaviour so that a



(101)

(102)



(103)

Reagents :-

(i) Benzene / 20 °C / stir / - 2h.

Scheme 18.

complete separation of the product from the excess of reagent was not possible, even by m.p.l.c.. This problem was surmounted by selective chemical removal of the excess of 9,10-phenanthraquinone by reaction with trimethyl phosphite without harming the cyclazine product. Some work by Ramirez[45] and his co-workers on phosphorane chemistry described how ortho-quinones, including 9,10-phenanthraquinone, reacted with trimethyl phosphite to form a pentaoxyphosphorane (103) (scheme 18). This reaction had the advantage of being selective for 9,10-phenanthraquinone (101), without effect on the cyclazine product. Chromatographic isolation of the cyclazine was then straightforward.

Thus a dehydrogenating reagent for the last step of the new synthetic pathway to a [3.3.3]cyclazine derivative had been found, and the yields from 4-chloroquinolizinylium perchlorate (44) revealed that this new synthetic route was already an improvement on the previous one[22], which had given a 47% yield. The only isolation required was of the dihydrocyclazines, prior to the dehydrogenation step.

2.4 "One-pot" synthesis of a [3.3.3]cyclazine derivative

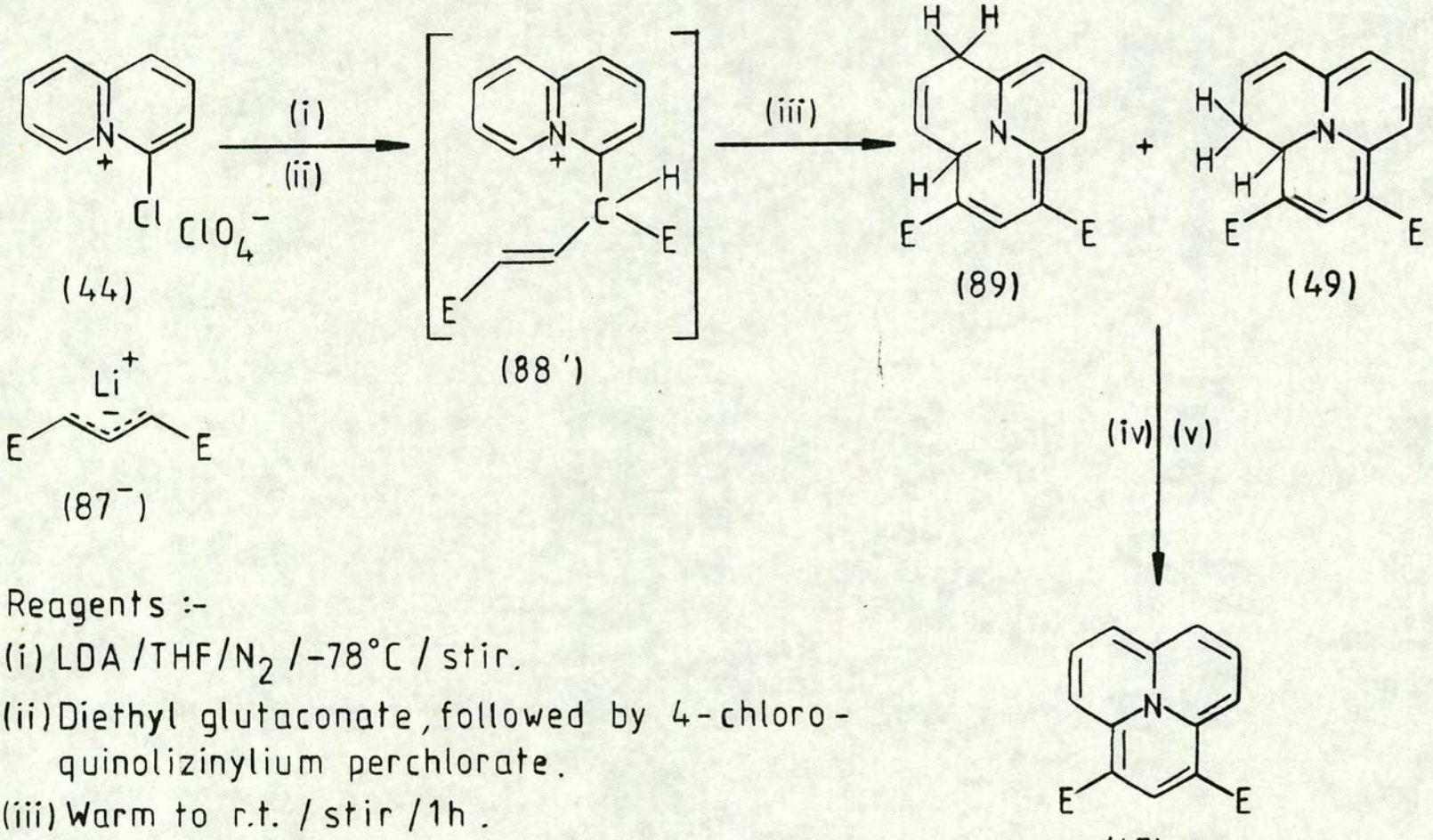
The ultimate aim of this work was to devise a shorter, more efficient route to the [3.3.3]cyclazine nucleus. Hence, a "one-pot" synthesis with no isolation of intermediates was an interesting target.

Based on the successful optimisation of the last two

steps (formation and dehydrogenation of the dihydro intermediates), it was felt that if these improved yields could be sustained through the dehydrogenation step, without isolation, then a "one-pot" synthesis could be developed. After a number of trial runs, this objective was in fact achieved and the following standard procedure was adopted.

The anion of diethyl glutaconate (87^-) was generated *in situ* using LDA in THF at -78°C under a nitrogen atmosphere, prior to addition of the 4-chloroquinolizinylium salt (44) in small aliquots at the same low temperature. After complete addition of (44), the stirred mixture was allowed to come to room temperature, before adding a slight excess of 9,10-phenanthraquinone (101) (1.2 equivalents), and the mixture was refluxed for three hours. Trimethyl phosphite was added to the hot solution which was then allowed to cool. The solution was filtered and the cyclazine isolated by flash column chromatography on neutral alumina. Yields of recrystallised 1,3-di-(ethoxycarbonyl)[3.3.3]cyclazine (47a) obtained by this procedure are generally greater than 54%, and typically 55-60%, based on the 4-chloroquinolizinylium salt (44). In one case an 83% yield of cyclazine was achieved by this new "one-pot" synthesis. Similar yields are possible in larger scale preparations by this much simplified procedure.

Thus one of the main objectives of this work has been achieved in the form of a "one-pot" synthesis of a [3.3.3]-


(i)
(ii)
(iii)
(iv)
(v)
(44)
(88')
(89)
(49)
(87⁻)
(47)
Reagents :-
(i) LDA / THF / N_2 / -78°C / stir.
(ii) Diethyl glutaconate, followed by 4-chloro-quinolizinylium perchlorate.
(iii) Warm to r.t. / stir / 1h.
(iv) a). 9,10-Phenanthraquinone (101) [1·2 equiv.] / - reflux / 3h.
b). $P(OMe)_3$ / stir / r.t. / 1h.
(v) Alumina flash column.
e.g. 83%.

Scheme 16B.

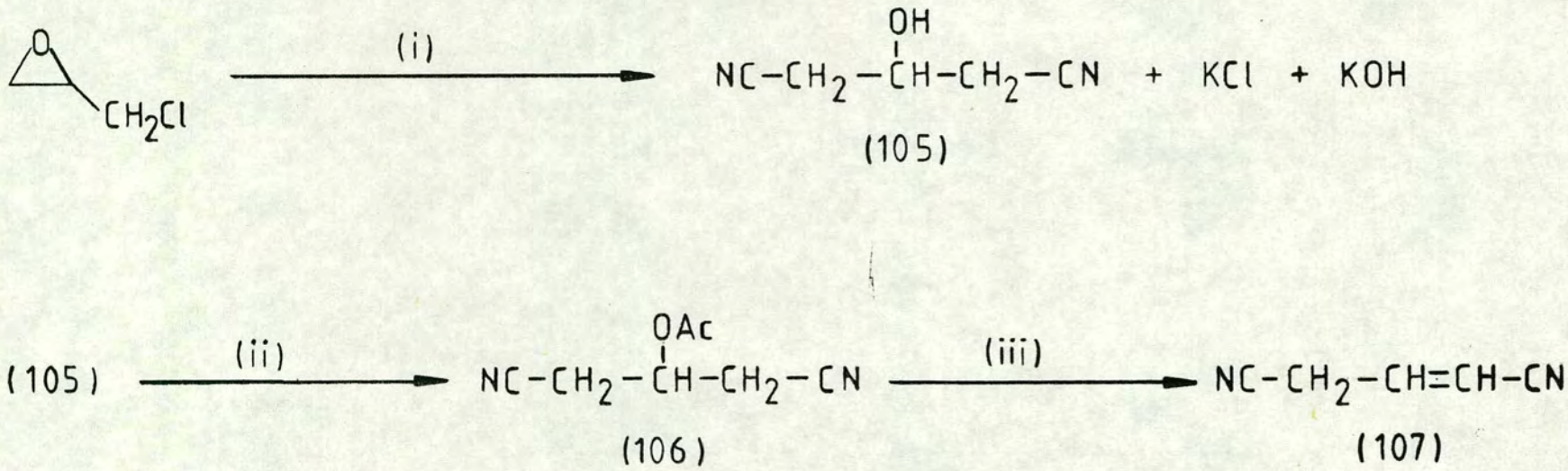
cyclazine derivative in yields higher than that obtainable by the previous route.

2.5 Synthesis of other [3.3.3]cyclazine derivatives

After the successful application of the propene derivative approach to [3.3.3]cyclazines (scheme 16) for diethyl glutaconate, this route was further tested to investigate the possibilities for the synthesis of other [3.3.3]cyclazine derivatives.

The new route was first adapted to synthesise the 1,3-dicyano[3.3.3]cyclazine (104), by using glutacononitrile (1,3-dicyanopropene) (107) as the three-carbon component. This propene derivative was prepared by a combination of several modified literature procedures[46] as outlined in the reaction scheme (scheme 19). β-Hydroxyglutaronitrile (105) was obtained by the reaction of epichlorohydrin with potassium cyanide[46a]. This hydroxy compound was then acetylated[46b] with acetic anhydride in pyridine. The final step to glutacononitrile was a modification of that of Johnson et al[46] who used a vertical furnace filled with glass helices at 450°C to obtain glutacononitrile (107) from the acetoxy compound (106) in 58% yield. In this present work, the use of preparative flash vacuum pyrolysis (FVP) at 700°C converted the acetoxy compound (106) smoothly into a mixture of E- and Z-glutacononitrile in 74% yield.

For the synthesis of 1,3-dicyano[3.3.3]cyclazine, the freshly prepared mixture of E- and Z-glutacononitrile



Reagents :-

(i) 2 KCN / H_2O / 60%.

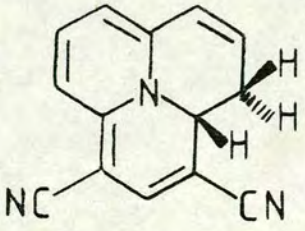
(ii) Ac_2O / pyridine / 75%.

(iii) Fvp / 700°C / high vacuum / 74%.

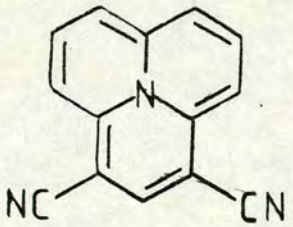
Scheme 19.

was used in place of diethylglutaconate in the optimised procedure described in section 2.3. As before, the first product isolated was a 3a,4-dihydro derivative (108) which was then dehydrogenated using 9,10-phenanthraquinone in refluxing toluene to give the 1,3-dicyano[3.3.3]cyclazine (104) in an overall 11% yield from 4-chloroquinolizinylium perchlorate (44). This yield is slightly higher than the previous synthesis[22], which gave the dicyano- compound in 10% yield by the longer cycloaddition route. It is likely, however, that the yield could be substantially improved since the optimum conditions for reaction of glutaconononitrile are not necessarily the same as those for the corresponding ester.

The 3a,4-dihydro compound was identified by its characteristic colour (purple as for the corresponding diester (49)) and by comparison of its ^{1}H n.m.r. spectrum with that of the diester (see Table 4/experimental section). The fully unsaturated 1,3-dicyano[3.3.3]cyclazine was identical with the product obtained by the previous route[22]. (^{1}H n.m.r., Table 5).



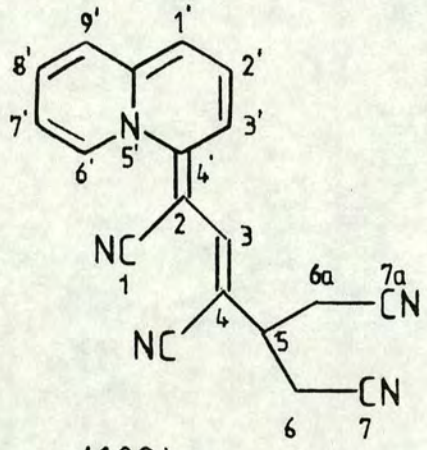
(108)



(104)

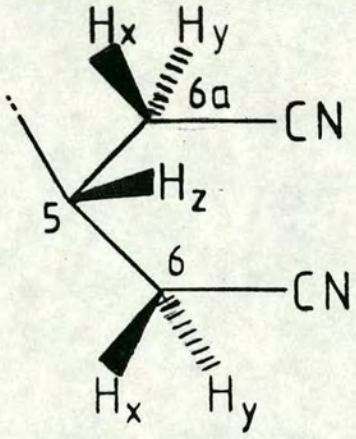
During the work up to obtain the dicyanodihydro-cyclazine, a polar by-product was isolated by preparative

t.l.c.. This compound was identified as a 4H-quinolizin--4-ylidene derivative (109) of an unsaturated tetranitrile which was probably formed by Michael addition of glutacononitrile to its own anion. Mass spectrometry showed a molecular ion at m|z = 311 as required for structure (109) and the n.m.r. (^{1}H and ^{13}C) spectra were in full agreement. The proton n.m.r. spectrum of (109)



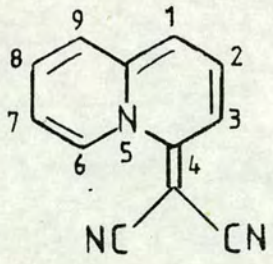
(109)

(Table 6; experimental section) [2-(quinolizin-4'-ylidene)-4-cyano-5-(cyanomethyl)hept-3-ene-1,7-dinitrile] showed a sharp singlet at δ 7.00 p.p.m. assigned to H-3, which would be deshielded by the 4-cyano group and possibly also by the quinolizine π-system. The quinolizine substructure was evident from the pattern of the high frequency resonances which compared well with the corresponding patterns in the spectra of the model quinolizine derivatives (110) and (111), particularly in relation to the H-6 and H-7 resonances. At the low frequency end of the spectrum of (109), the signals for the methylene protons at C-6 and C-6A showed non-equivalence, consistent with

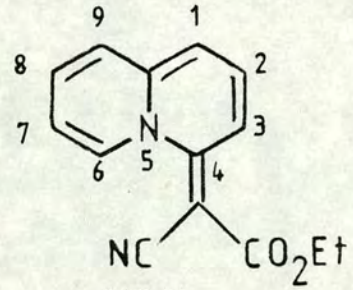


(109A)

their situation next to the prochiral centre at C-5 [see partial structure (109A)]. The geminal coupling constant $J_{x,y}$ (16.8 Hz) and the two vicinal coupling constants, J_{xz} and J_{yz} (8.8 and 6.5 Hz) were valuable in interpreting this part of the spectrum. The signal for the saturated



(110)

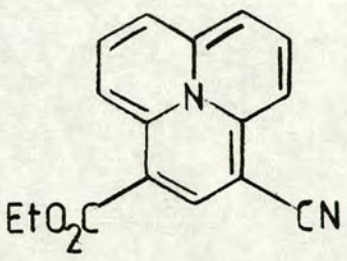


(111)

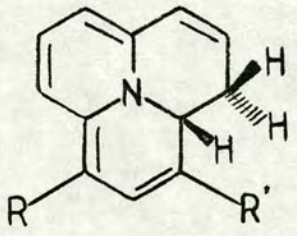
C-5 proton appeared as a triplet of triplets at δ 2.97 with the same 8.8 and 6.5 Hz coupling constants. The DEPT ($p\phi = 3\pi/4$) carbon-13 n.m.r. spectrum showed the expected CH_2, sp^3CH, and sp^2CH signals for the structure assigned (Table 6; experimental section).

A synthesis of the [3.3.3]cyclazine cyano ester (112) was also accomplished by this new synthetic route. Once

again, the low temperature LDA approach was used to generate the anion of ethyl 4-cyanobut-2-enoate, which was treated with 4-chloroquinolizinylium perchlorate (44) as before. The purple colour of the reaction mixture showed that the reaction was indeed occurring to give the dihydro compounds, but these were not fully characterised because of the possibility that isomers would be present (113). The yield for the isolated dihydro compound (m|z 226, as required for molecular ion) was about 38%. Dehydrogenation of this dihydro derivative was achieved by refluxing with 9,10-phenanthraquinone in dry toluene, to give the desired cyclazine (112) in 52% yield. This cyclazine was fully characterised by proton and carbon-13 n.m.r. and other spectroscopic techniques. Full details may be found in the experimental section [Table 7].



(112)



(113)

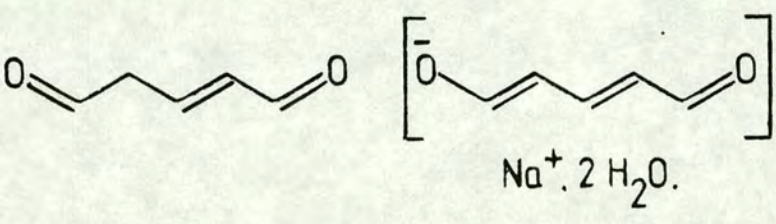
a : R = CN, R' = CO_2Et.

b : R = CO_2Et, R' = CN.

The applicability of the new route to [3.3.3]cyclazine derivatives was further tested with two other 1,3-disubstituted propenes.

Glutacondialdehyde (114) was synthesised as its

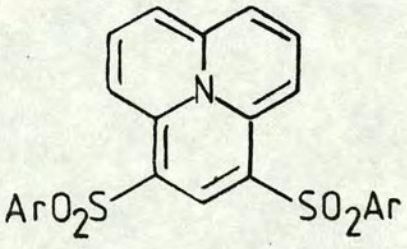
sodium salt dihydrate[47] (115), in which form it is more stable than as the free aldehyde. When this salt was reacted directly with 4-chloroquinolizinylium perchlorate (44) at room temperature, or at lower temperatures in acetonitrile or DMF, a number of products were formed in



(114) (115) (116)

very low yield, as noted by analytical tlc. None of these products was isolated or showed the type of chromatographic behaviour expected of the cyclazine (116) or its dihydro-derivatives. No conclusions may be drawn from this particular set of experiments, but it seems possible that the reaction failed because of the low nucleophilicity of the glutacondialdehyde anion (115). The charge in this anion is probably located mainly on the electronegative oxygen atoms, and such an arrangement would not favour [3.3.3]cyclazine formation, which requires nucleophilic attack by a carbanion at the C-4 position of the 4-chloroquinolizinylium salt (44).

An attempt to synthesise a 1,3-di(p - tolylsulphonyl)-[3.3.3]cyclazine (117) also met with little success. The anion of 1,3-di(p-tolylsulphonyl)propene[48] (118) was generated by treatment with either LDA or with butyl



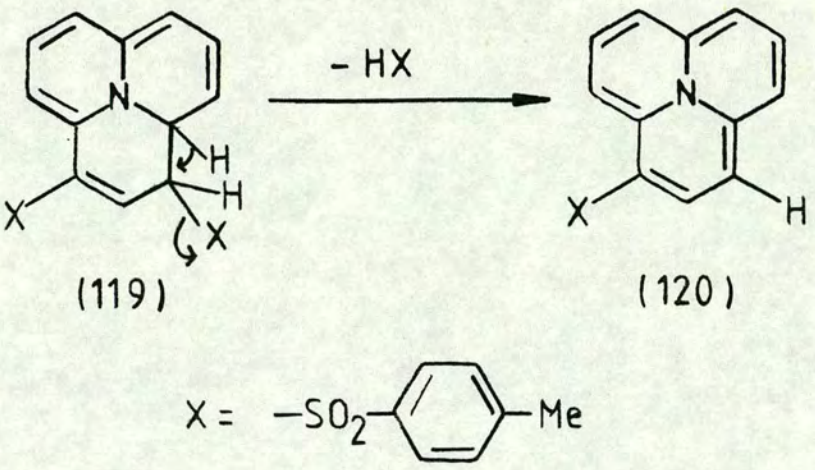
(117)

$ArO_2S-CH_2-CH=CH-SO_2Ar$

(118)

Ar = p-MeC_6H_4-

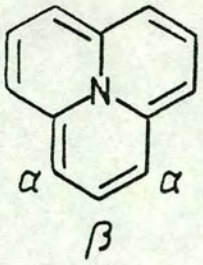
lithium and the chloroquinolizinylium salt (44) was added in the usual manner. Trace products that could possibly have been the required cyclazine (117) and its 3a,4-dihydro derivative were then visible by analytical tlc. An attempt was made to isolate the suspected cyclazine (a yellow band) by preparative tlc, but decomposition appeared to be taking place, and it was not possible to obtain the product sufficiently pure for characterisation. The low yields in this reaction may be due to the steric effect of the bulky p-tolylsulphonyl groups which could hinder electrophilic attack at the adjacent anionic centres of the propene derivative (118). It is also possible, however, that the reaction was diverted from its normal course by the propensity of the p-tolylsulphonyl group to act as an anionic leaving group in elimination reactions. If the dihydrocyclazine isomer (119) was formed, then it could have lost one molecule of p-toluenesulphinic acid, as an alternative to dehydrogenation, thus generating a [3.3.3]cyclazine (120) with only one stabilising group (scheme 20). These latter types of [3.3.3]cyclazine are



Scheme 20.

reported by Leaver et al[22] to be of limited stability in the presence of air. A large amount of dark baseline material was evident by t.l.c. and during column chromatography.

As discussed in the introduction, [3.3.3]cyclazines are stabilized by electron-withdrawing substituents (E.W.) in the α-positions of the ring. E.W.-substitution at any of the β-positions of the cyclazine skeleton is likely to have the opposite effect, but there are few experimental observations to confirm this. In the current work two

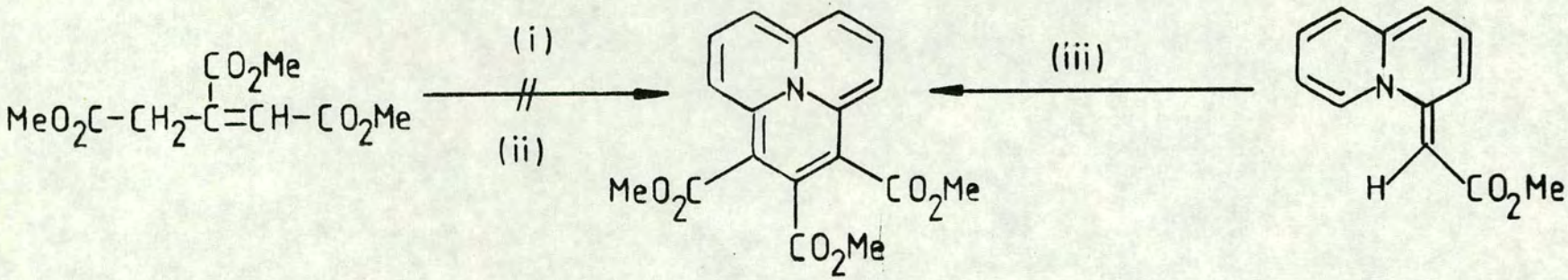


(3)

attempts were made to synthesise 1,2,3-trisubstituted [3.3.3]cyclazines starting with 1,2.3-trisubstituted propenes and by using the improved route. In one case the 2-substituent of the propene was electron-withdrawing (CO_2Me) and in the other electron-releasing (Me).

Trimethyl aconitate (1,2,3-tri(methoxycarbonyl)-prop-1-ene) (121) appeared to be a good propene derivative to try, since the 1,2,3-trisubstituted [3.3.3]cyclazine (122) that would result is already known, having been synthesised previously[22] by the cycloaddition route (scheme 21). However, when the 4-chloroquinolizinylium salt (44) was added to the lithium enolate of trimethyl aconitate in THF, no trisubstituted cyclazine or dihydro-cyclazine was obtained. The reaction mixture became very dark in colour and work-up led to a substantial recovery (~60%) of the quinolizinylium salt (44). T.l.c. analysis of the reaction mixture revealed no fast moving products but only materials of low chromatographic mobility. No satisfactory reason can be given for the failure of this reaction.

The second 1,2,3-trisubstituted propene to be tested as a three carbon component was dimethyl β-methyl-glutaconate (124) and more favourable results were obtained here (scheme 22). Using the "one-pot" procedure as developed for diethyl glutaconate, the cyclazine (126) was isolated as a purple solid after flash column chromatography. This cyclazine was unstable on t.l.c. plates (silica and alumina) and it is suspected that losses during the flash



(121) (122) (123)

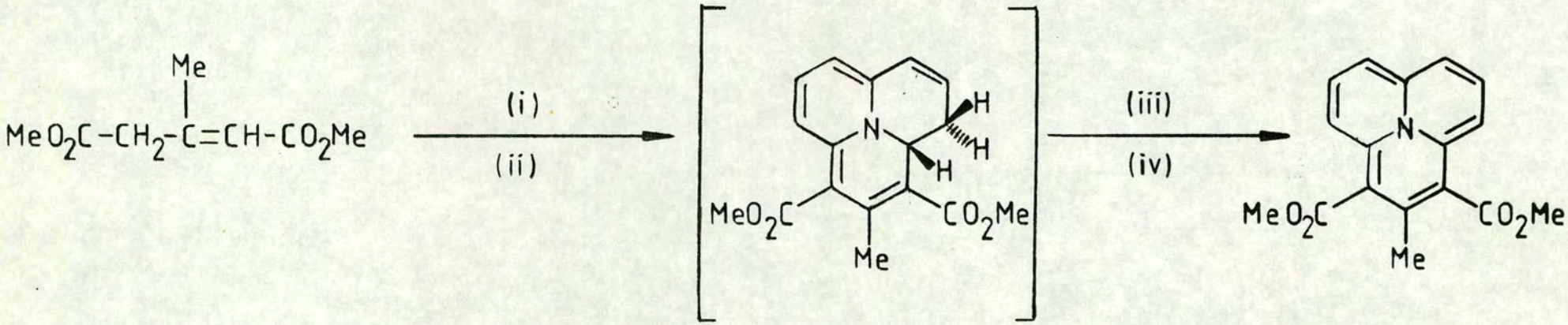
Reagents :-

(i) LDA / 78°C / THF / N_2 / (44).

(ii) △ / THF.

(iii) DMAD/benzene / 10°C / 23%, followed by $PhNO_2$ / reflux / 10 min. / 8% [ref. 22].

Scheme 21.



(124) (125) (126)

Reagents :-

(i) LDA /-78°C / N_2 / THF.

(ii) 4-Chloroquinolizinylium perchlorate .(44) / -78°C to r.t..

(iii) 9,10-Phenanthraquinone (101) / THF / reflux / 3h.

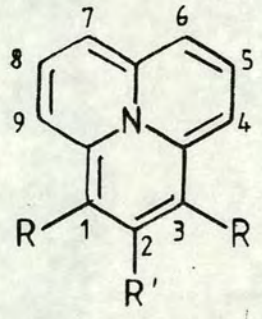
(iv) $P(OMe)_3$/ flash column [alumina].

Scheme 22.

column purification were substantial. Staining of the column (neutral alumina) was evident as was the formation of a green solid that was not identified. Careful recrystallisation of the crude purple solid from THF/cyclohexane gave 1,3-di(methoxycarbonyl)-2-methyl[3.3.3]-cyclazine (126) as purple-brown needles (34%), that decomposed in higher boiling solvents.

It is interesting to compare this cyclazine derivative (126) with other substituted cyclazines by using proton n.m.r. (Table 8). The table compares several [3.3.3]cyclazine derivatives, that have various types of substituent in α- and β- positions of the cyclazine skeleton, using their proton chemical shifts. The spectrum of the 2-methylcyclazine derivative (126) shows a general shift to low frequency at all positions relative to the parent diester compound (47). This shielding effect on the ring protons is probably attributable to the steric bulk of the methyl group in the 2-position which causes the ester groups in the C-1 and C-3 positions to twist out of planarity with the ring structure, thus removing some of the potential for delocalisation of the ring π-electron density into these substituents. Hence an overall shielding effect is observed, the paratropicity of the [3.3.3]cyclazine ring system being noticeably enhanced. A similar effect is observed for the 2-phenyl derivative (127)[22] as expected, although the shielding effect in the latter compound is not as great as that in its methyl counterpart. It is also interesting to compare the 2-methyl derivative

Table 8. ^{1}H n.m.r. spectrum comparison of compounds (47a), (126), (127), (122) and (128)



Compound	δ/H a) H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	J/Hz
(47a) b) R=CO_2Et, R'=H	(1.18) (3.99)	7.09	(1.18) (3.99)	6.68	6.08	5.21	5.21	6.08	6.68	$J_{4,5}=J_{5,6}=8.1$ $J_{4,6}=1.7$
(126) R=CO_2Me, R'=Me	(3.51)	(1.16)	(3.51)	4.64	5.47	4.42	4.42	5.47	4.64	$J_{4,5}=J_{5,6}=8.2$ $J_{4,6}=1.3$
(127) b) R=CO_2Me, R'=Ph	(2.91)	(6.7-7.3)	(2.91)	4.99	5.57	5.54	5.54	5.57	4.99	$J_{4,5}=J_{5,6}=8$ $J_{4,6}=2$
(122) b) R=R'=CO_2Me	(3.45)	(3.60)	(3.45)	6.20	6.14	5.33	5.33	6.14	6.20	N/A
(128) b) R=CO_2Et, R'=H, 5-Me	(1.18) (4.01)	7.33	(1.18) (4.01)	6.78	(1.65)	5.24	5.31	6.16	6.76	$J_{7,8}=J_{8,9}=8.3$ $J_{4,6}=1.5$, $J_{7,9}=1.6$

a) All chemical shifts measured in $CDCl_3$/ Values in parenthesis indicate substituent groups.

b) data taken from ref. 22.

(126) with the 5-methyl derivative (128)[22], especially with respect to the C-Me signal (a singlet). In the 2-methyl case, the singlet occurs at δ1.16 p.p.m. compared with δ1.65 for the 5-methyl compound. Once again, this may be due to an enhanced paramagnetic ring current in the 2-methyl compound (126), though there could be some contribution to the shielding of this methyl group from the ester carbonyl groups, depending on the extent of their deviation from coplanarity with the ring system.

The enhanced paratropicity of the 2-methyl 1,3-diester relative to the 1,3-diester itself suggests an increase in "antiaromatic" character and is thus consistent with the chemically unstable nature of this compound.

2.6 Summary

The new shorter route to [3.3.3]cyclazine derivatives is applicable, not only to the use of diethyl glutaconate as the propene, but also for other propene derivatives as has been shown here. Some of these preparations could probably be improved in yield by development work to optimise the conditions individually for each reaction. However, one of the aims of the current work in finding a broadly applicable and better route to [3.3.3]cyclazine derivatives has been attained.

SECTION 3

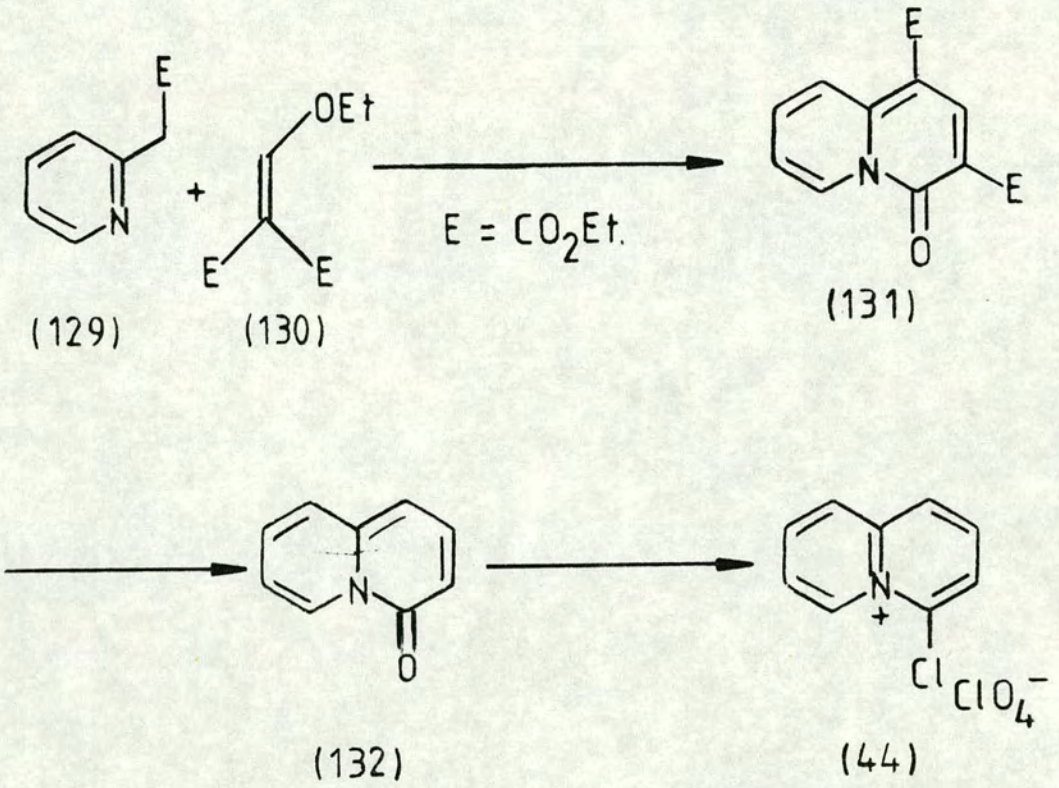
3. Investigation of a quinolizinethione as a potential precursor of a [3.3.3]cyclazine.

3.1 Introduction

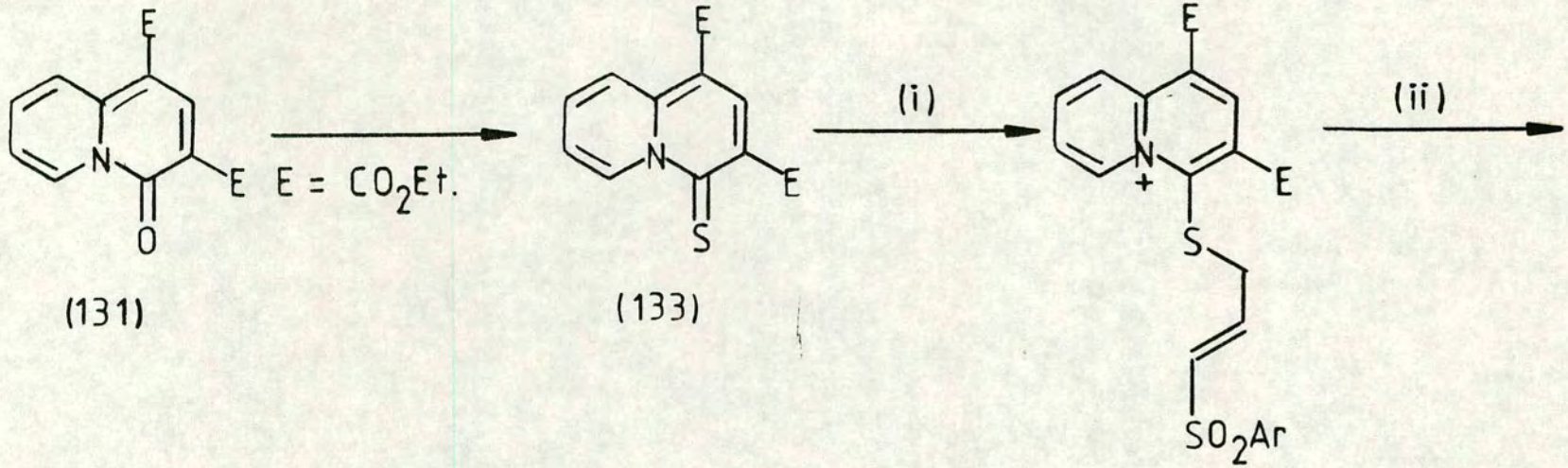
The original cycloaddition route[22] to [3.3.3]cyclazines and the newer cyclisation route (section 2) both start from an unsubstituted bicyclic precursor [the salt (44)] and depend, for their success, on the incorporation of two electron withdrawing substituents during the construction of the third component ring of the cyclazine skeleton. It is, however, possible to envisage an alternative strategy in which the two EWG substituents are already present at the bicyclic stage, the third ring being constructed in an unsubstituted form. The advantage of this approach would lie in its potential for direct utilisation of an earlier intermediate (131) in the synthetic pathway leading to the chloroquinolizinylium salt[49] (44) (scheme 23).

In a sense, both of the existing syntheses of [3.3.3]cyclazines are wasteful in that the two correctly positioned ester groups in the quinolizinone (131) are removed, only to be reintroduced in another ring at another stage (scheme 16).

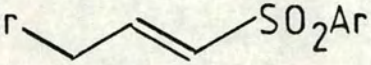
The proposed pathway to the [3.3.3]cyclazine-1,3-diester (47) from the quinolizinone (131) is outlined in scheme 24, and, like the newly developed route described



Scheme 23.



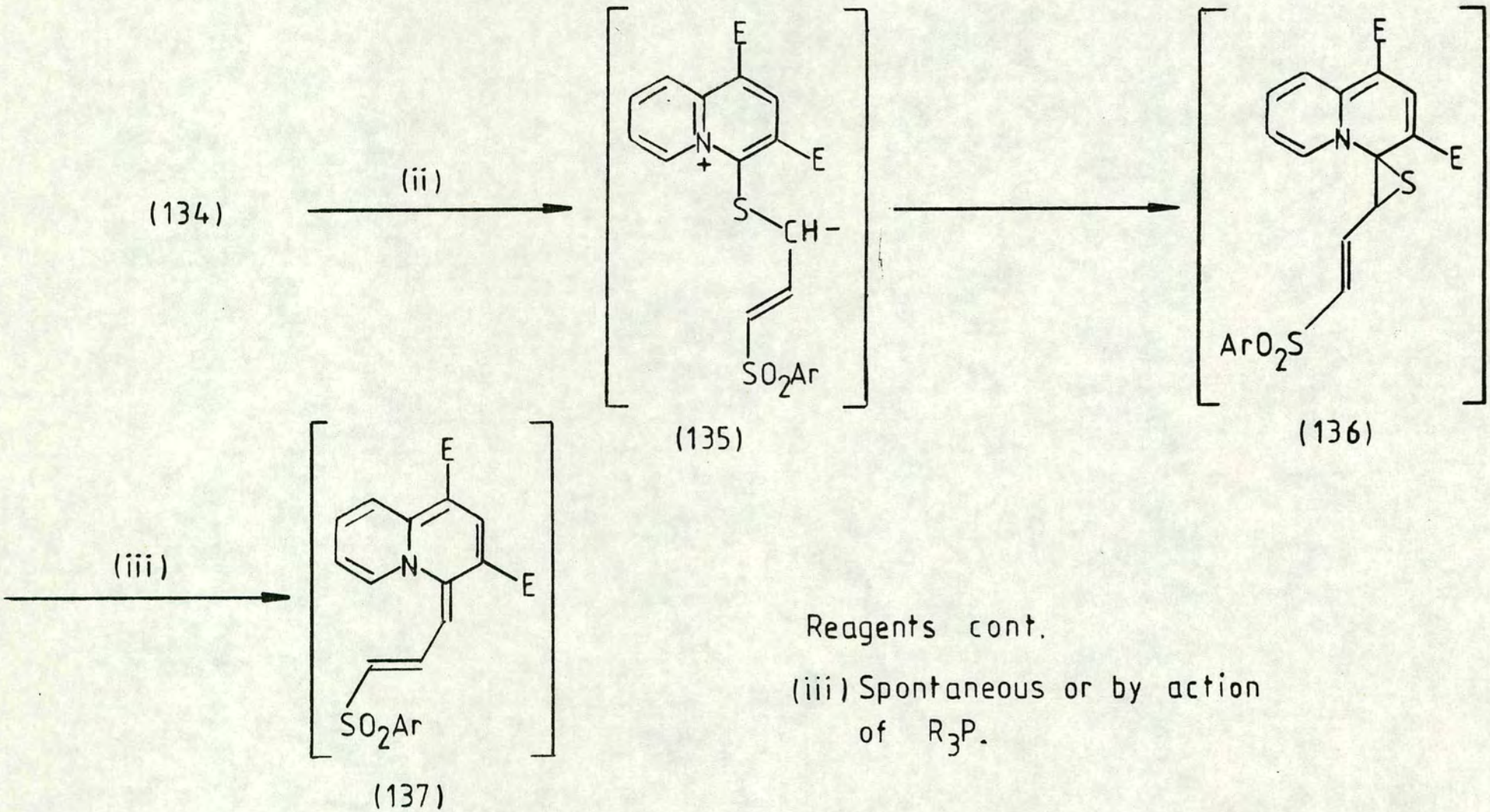
Reagents [proposed]:-

(i) 

(ii) Base.

Scheme 24.

cont.

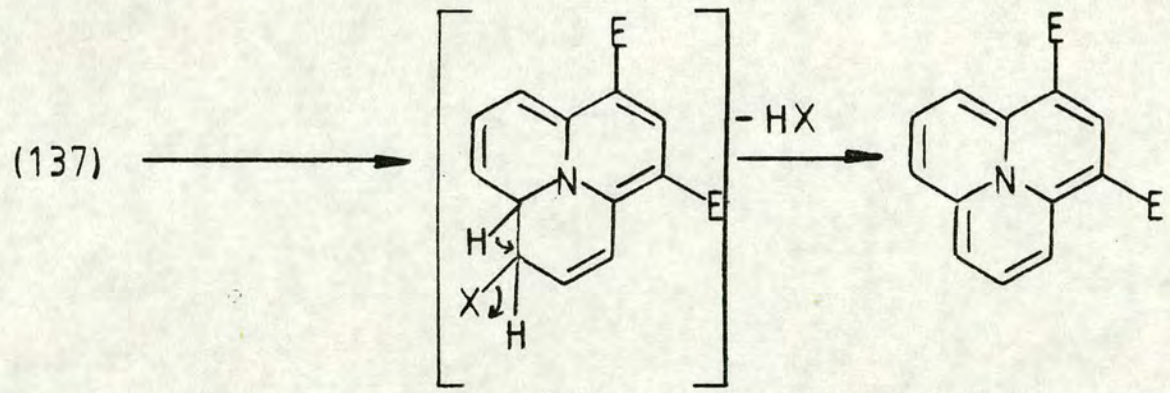


Reagents cont.

(iii) Spontaneous or by action of R_3P.

Scheme 24 . cont,

earlier, involves an electrocyclic cyclisation of a quinolizin-4-ylidene propene (137). The steps leading to this intermediate depend on the S-allylation of the quinolizinethione derived from the starting material, followed by extrusion of sulphur. This type of reaction was originally reported by Knott[50] and was later used to great effect by Eschenmoser[51] in his synthesis of Vitamin B_{12}. An activating group would be required to facilitate deprotonation of the S-allyl group prior to episulphide ring closure and it was proposed that this should be a phenylsulphonyl group in the γ-allylic position. This group would then be eliminated (as benzenesulphinic acid) after cyclazine ring closure, thus avoiding the need for a dehydrogenating step.



Scheme 24a cont.

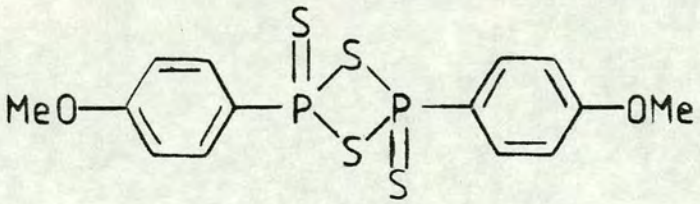
Unfortunately, a detailed investigation of these proposals was precluded since no high-yielding method was found for the conversion of the substituted quinolizinone

(131) into the corresponding thione (133). Nevertheless, some interesting results emerged during the search for such a method and this part of the investigation will now be described.

3.2 Attempts to prepare a 4H-quinolizine-4-thione derivative

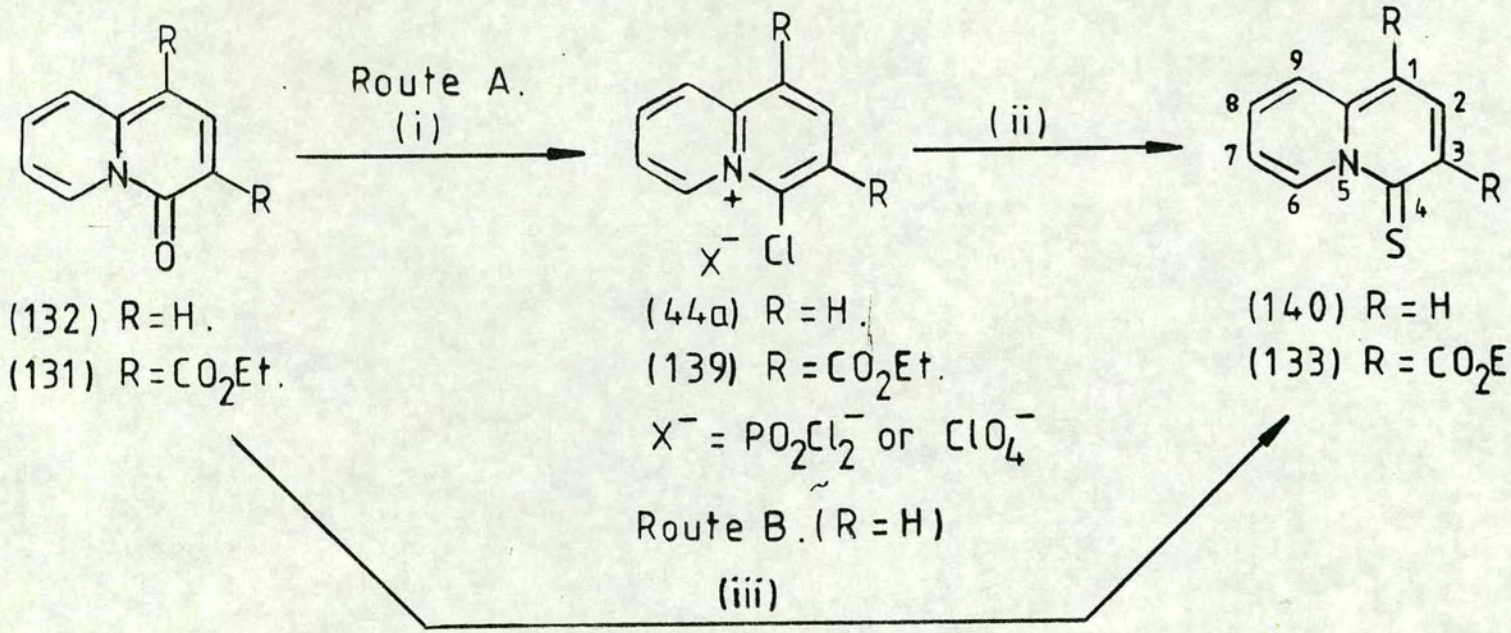
Quinolizine-4-thione (140) was first prepared by Boekelheide and Lodge[83] by heating the corresponding quinolizinone (132) with phosphorus pentasulphide (scheme 25).

When the above method was applied to the 1,3-di-(ethoxycarbonyl)quinolizinone (131), an orange solid was obtained in very low yield, which was shown by mass spectrometry to have a molecular ion at m/z 305 as required for replacement of one oxygen by sulphur. Lawesson's reagent[52] [2,4-bis(4-methoxyphenyl)-1,3-dithia--2,4-diphosphetane-2,4-disulphide] (141) gave the same



(141)

orange solid in yields of 7% to 20%, depending on the conditions employed. The orange solid was identified by spectroscopic techniques.



(132) R = H.
(131) R = CO_2Et.

(44a) R = H.
(139) R = CO_2Et.
$X^- = PO_2Cl_2^-$ or ClO_4^-

(140) R = H
(133) R = CO_2Et.

Route B. (R = H)

(iii)

Route A.

R = H, (i) $POCl_3$ / △ / 10min., $HClO_4$(aq.)
(ii) $Na_2S.9H_2O$(aq) / 3h / r.t. / 70 %
or
Thiourea / EtOH / reflux / 1h then
10 % NaOH / NaCl / $CHCl_3$ extr. / 40%.

Route B.

R = H, (iii) P_2S_5 / △ / 57 %.

Scheme 25.

The ^{13}C n.m.r. spectrum of this thiocarbonyl compound was very similar to that of the starting material (Table 9), the main difference being in the high frequency region where one of the two ester carbonyl resonances (δ164.4 and 165.0) present in the starting material (131) was replaced by a peak at δ208.9 attributable to thiocarbonyl. The resonance at δ155.1 due to the ring carbonyl was shifted only slightly (to δ154.2). This result suggested that one of the ester carbonyl groups had been converted into a thioester. Confirmation of this result was obtained by comparison of the observed thiocarbonyl shift with that calculated from Lawesson's empirical equation[52-54] (equation 1) for ester thiocarbonyl groups[53]. This and related equations were derived by Lawesson et al during their early studies of thionation reactions with compound (141). Thus the

$$\delta_{(c=s)} = 1.75\ (\delta_{(c=o)}) - 79.70 \qquad \ldots(1)$$

value of $\delta_{(c=s)}$ calculated to correspond to the ester carbonyl chemical shift ($\delta_{(c=o)}$) at 165.0 p.p.m. is 209.0, in excellent agreement with the experimental value of 208.9.

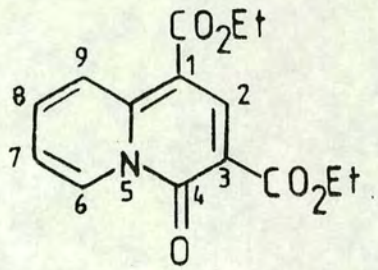
The ^{1}H n.m.r. spectrum of the orange solid showed a small shift of the H-2 resonance relative to the starting quinolizinone derivative (131), but no appreciable shift of H-9 (Table 10;experimental section), thus showing that the thioester group was present at C-3 rather than C-1. Further evidence for the thioester group being in position-3 comes from its effect in shifting the resonance frequency of C-3 rather than C-1 [from δ105.4 p.p.m. for

Table 9. ^{13}C n.m.r. spectral data for compounds (131), (133) and (142) [a)]

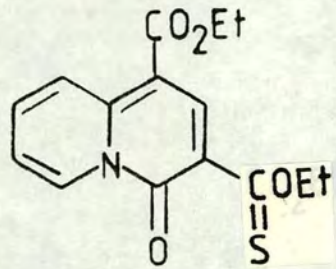
parent (131)		thioester (142)		thione (133)	
δ/ppm	ass.	δ	ass.	δ	ass.
14.1	sp^3CH_3	13.6	sp^2CH_3	13.8	sp^3CH_3
14.2	sp^3CH_3	14.1	sp^3CH_3	14.1	sp^3CH_3
60.7	sp^3CH_2	60.8	sp^3CH_2	61.4	sp^2CH_2
60.8	sp^3CH_2	68.3	sp^3CH_2	61.7	sp^2CH_2
101.5	sp^2C_1	101.8	sp^2C_1	109.2	sp^2C_1
105.4	sp^2C_3	115.5	sp^2C_3	119.2	sp^2CH
117.3	sp^2CH	117.3	sp^2CH	124.8	"
124.1	"	124.1	"	130.2	sp^2C_3
130.0	"	130.4	"	132.7	sp^2CH
136.4	"	136.2	"	134.7	"
144.0	"	144.0	"	135.0	"
146.8	sp^2C_{9A}	146.1	sp^2C_{9A}	144.8	sp^2C_{9A}
155.1	sp^2C=O ring	154.2	sp^2C=O ring	164.1	sp^2C_1'=O
164.4	sp^2C=O ester	164.5	" ester	167.0	sp^2C_3'=O
165.0	sp^2C=O ester	208.9	sp^2C=S	173.3	sp^2C_4=S

a) In $CDCl_3$ at 50.32 MHz

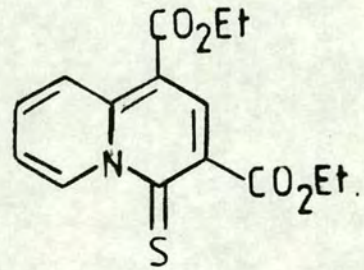
Table 10. ^{1}H n.m.r. spectra[a] of compounds (131), (133) and (142)



(131)[b]



(142)[b]

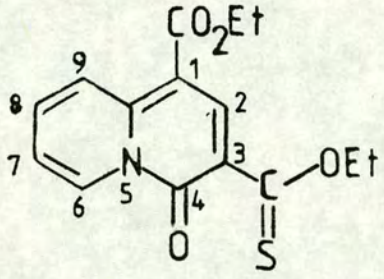


(133)[c]

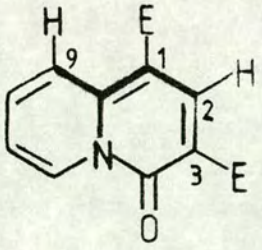
Assign/δ_H[a]	(131)[b]	(142)[b]	(133)[c]
H-1	1.41 t 3H 4.38 q 2H	1.43 t 3H 4.40 q 2H	1.41 t 3H 4.41 q 2H
H-2	9.14 s 1H	9.34 s 1H	8.36 s 1H
H-3	1.41 t 3H 4.42 q 2H	1.55 t 3H 4.79 q 2H	1.42 t 3H 4.42 q 2H
H-6	9.51 "d"[d] 1H	9.54 "d"[d] 1H	10.75 d 1H
H-7	7.31 dt 1H	7.33 dt 1H	7.53 dt 1H
H-8	7.85 ddd 1H	7.85 ddd 1H	7.88 ddd 1H
H-9	9.35 "d"[d] 1H	9.37 "d"[d] 1H	9.46 d 1H
J/Hz	$J_{6,7}$ 7.1 Hz; $J_{6,8}$ 1.6 $J_{7,8}$ 6.9; $J_{7,9}$ 1.4 $J_{8,9}$ 9.1	$J_{6,7}$ 7.1 Hz; $J_{6,8}$ 1.6 $J_{7,8}$ 6.9; $J_{7,9}$ 1.5 $J_{8,9}$ 9.1	$J_{6,7}$ 7.0 Hz; $J_{6,8}$ 1.5 $J_{7,8}$ 7.1; $J_{7,9}$ 1.6 $J_{8,9}$ 9.1

a) In $CDCl_3$. b) At 80 MHz. c) At 200 MHz. d) Actually appears as a multiplet with doublet characteristics (d with fine splitting)

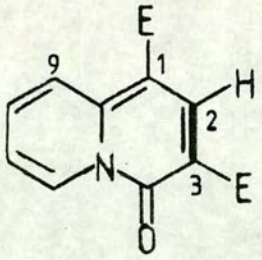
the diester (131) to 115.5 p.p.m. for the monothiodiester]. These two quaternary carbon resonances were distinguished by their differing intensities, C-3 giving the smaller signal because its relaxation is mediated by only one neighbouring proton (H-2), while that of C-1 is mediated by two such protons (H-2 and H-9).



(142)



(131A)



(131B)

Also evident from the proton n.m.r. spectrum was a shift to higher frequency (deshielding effect) for one set of signals corresponding to the saturated protons of one of the ester groups (see Table 10), thus providing further evidence for the thioester substituent. This evidence shows that the orange solid isolated from these experiments was the 3-(ethoxythiocarbonyl)derivative (142), and not the desired quinolizinethione.

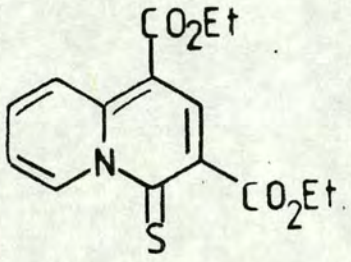
3.3 Preparation of a 4H-quinolizine-4-thione derivative

Quinolizine-4-thione can also be obtained by the procedure of Van Allan and Reynolds[49] who treated quinolizin-4-one with phosphoryl chloride ($POCl_3$) to obtain the chloroquinolizinylium salt (isolated as a perchlorate), and converted this into the thione with aqueous sodium sulphide (Na_2S) (scheme 25 [route A]). However, when the first step of this procedure was applied to the 1,3-di(ethoxycarbonyl) compound (131), starting material was recovered (80%) and no quinolizinylium salt was obtained. A similar result was observed when $POCl_3$ was replaced by oxalyl chloride [$(COCl)_2$]. Two possible explanations of these results may be (a) conversion to the chloroquinolizinylium salt (139) may be difficult owing to the electron withdrawing groups, or (b) the salt is formed but, being strongly electrophilic, reacts mainly with water to regenerate the quinolizinone. Since no attempt had been made to characterise the unstable perchlorate obtained after reaction with $POCl_3$, it is not clear which of these explanations is correct.

To minimise the opportunities for possibility (b), the reaction using $POCl_3$ was repeated, but no attempt was made to convert the resulting salt into a perchlorate. Instead the salt [presumed to be a 4-chloroquinolizinylium dichlorophosphate (139)] was precipitated from the reaction mixture by the addition of dry ether. The rapidly filtered precipitate was then treated directly with an excess of

Na_2S in DMF, which gave the required 4H-quinolizine-4-thione derivative, but only in very low yields (ca. 7%), along with some of the starting material.

The spectroscopic evidence for the quinolizine-4-thione derivative (133) is as follows. The mass spectrum of the golden-yellow needles showed a molecular ion at m|z 305 ($p^{+\cdot}$)



(133)

as expected. Fragment ions at m|z 233 and 159 were due to the loss of one ester group and both ester groups respectively. The n.m.r. evidence (proton and carbon-13) was more decisive (Tables 9, 10). The carbon-13 n.m.r. spectrum of this compound (113) [Table 9] revealed several interesting points, and once again, the chemical shifts at the high frequency end of the spectrum could be compared directly to those of the 1,3-di(ethoxycarbonyl)-quinolizin-4-one starting material. The carbonyl resonances for the thione occurred at δ164.1, 167.0 and 173.3 corresponding to the two esters and the ring thio-carbonyl, respectively, while the corresponding resonances for the quinolizinone (131) were δ164.4, 165.0 and 155.1 p.p.m.. Application of Lawesson's formula for N,N-dialkyl-thioamides[54] (equation 2), using the value of 155.1 for

$\delta_{(C=O)}$, gives a calculated value of

$$\delta_{(C=S)} = 1.60\ (\delta_{(C=O)}) - 72.30 \qquad \ldots(2)$$

$\delta_{(C=S)}$ = 175.8 p.p.m. This value is only 2.5p.p.m. different from the experimental value, in good agreement with the quinolizine-4-thione structure (133). Another interesting point about the ^{13}C n.m.r. spectrum of (133) is that the C-1 and C-3 signals have shifted to δ109.2 and 130.2 relative to δ101.5 and 105.4 in the quinolizinone. Thus, the thiocarbonyl moiety in the C-4 position deshields the nearer C-3 carbon to a greater extent than the more remote C-1 carbon, as would be expected.

The proton n.m.r. spectrum of the quinolizinethione revealed strong deshielding of H-6 (by >1.2 p.p.m.), relative to H-6 of the starting quinolizinone (131). This is consistent with the presence of the thiocarbonyl group in the C-4 position. Also noticeable is the shift of the H-2 singlet from δ9.14 [in (131)] to δ8.36 in the thione.

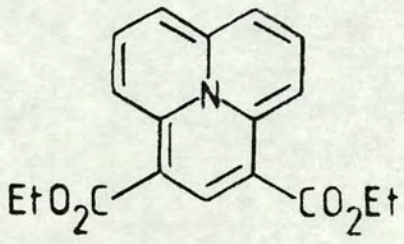
Thus, to summarise; the yields found for the synthesis of the quinolizinethione (133) from the quinolizinone (131) were low(7%) and, since this was only the first step of a possible synthetic pathway to [3.3.3]cyclazine derivatives (scheme 24) it did not seem worthwhile to continue further.

SECTION 4

4. Chemistry of a [3.3.3]cyclazine derivative

4.1 Introduction

Following the success of the new route to [3.3.3]-cyclazines from 4-chloroquinolizinylium perchlorate (44) and activated propenes, attention was now turned to the second aim of this project, namely to investigate further aspects of the chemistry of [3.3.3]cyclazines. For most of this work, 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine (47a) was used as the substrate, this compound being readily available in multigram quantities using the new approach.



(47a)

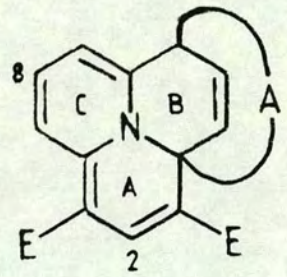
One part of this work (section 4.2) was centred on potential cycloaddition reactions of the cyclazine (47a) and may be subdivided into three areas: (i) further investigations of Diels-Alder cycloaddition reaction with stable dienophiles; (ii) studies on the possible synthesis of benzo[3.3.3]cyclazine derivatives via the addition of the short-lived reactive intermediate, benzyne; and

(iii) the possibility of ring expansion of the [3.3.3]cyclazine nucleus based on carbene addition. This last area of investigation was envisaged as being possibly relevant to a synthesis of the unknown [3.4.4]cyclazine ring system. On several occasions during this part of the work, the product or products that resulted arose not from a cycloaddition reaction, but from a substitution reaction, usually at the C-4 and/or C-6 position(s) of the ring. This type of reaction has been reported[22] before, and is covered in a small section of the introduction to this thesis.

A second part (section 4.3) of this investigation into the reactivity of [3.3.3]cyclazines was concerned with some new oxidation reactions of the [3.3.3]cyclazine diester (47a) and finally some observations are described (section 4.4) that do not fall into either of the foregoing categories.

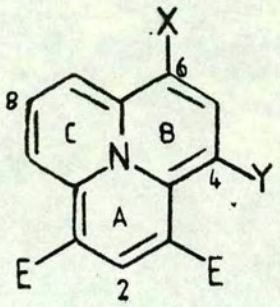
In assigning structures to products, either as cycloadducts (143) or as substitution products (144), a number of characteristic features have proved generally useful in this work. These features are listed below in order to simplify the subsequent discussion of individual experiments by reducing the need for repetition.

(i) Whereas cycloadducts (143) are invariably clear red and show one broad absorption band in the visible region (λ_{max} ~ 510 nm) with $\log_{10}\varepsilon < 4$, substitution products exhibit various colours, all with shades of brown, and generally show two visible absorption bands



(143)

A = group derived from dienophile.



(144)

X or Y = substituent.

(λ_{max} ~400-410 and 450-550 nm), both with $\log_{10}\varepsilon > 4$.

(ii) Both types of product (143) and (144) show an AMX spin system (ring C protons) and a singlet (H-2) in their proton n.m.r. spectra, but the chemical shifts (δ) of these resonances are higher (by ~ 1 p.p.m. on average) for cycloadducts than for substitution products. In addition, the H-8 signal appears as a doublet of doublets for cycloadducts but as a triplet for substitution products.

(iii) The n.m.r. signals for the protons of ring B are present as a simple AX spin system for substitution products. This is absent in the spectra of cycloadducts, being replaced by an ABX system due to the protons of the bridged ring.

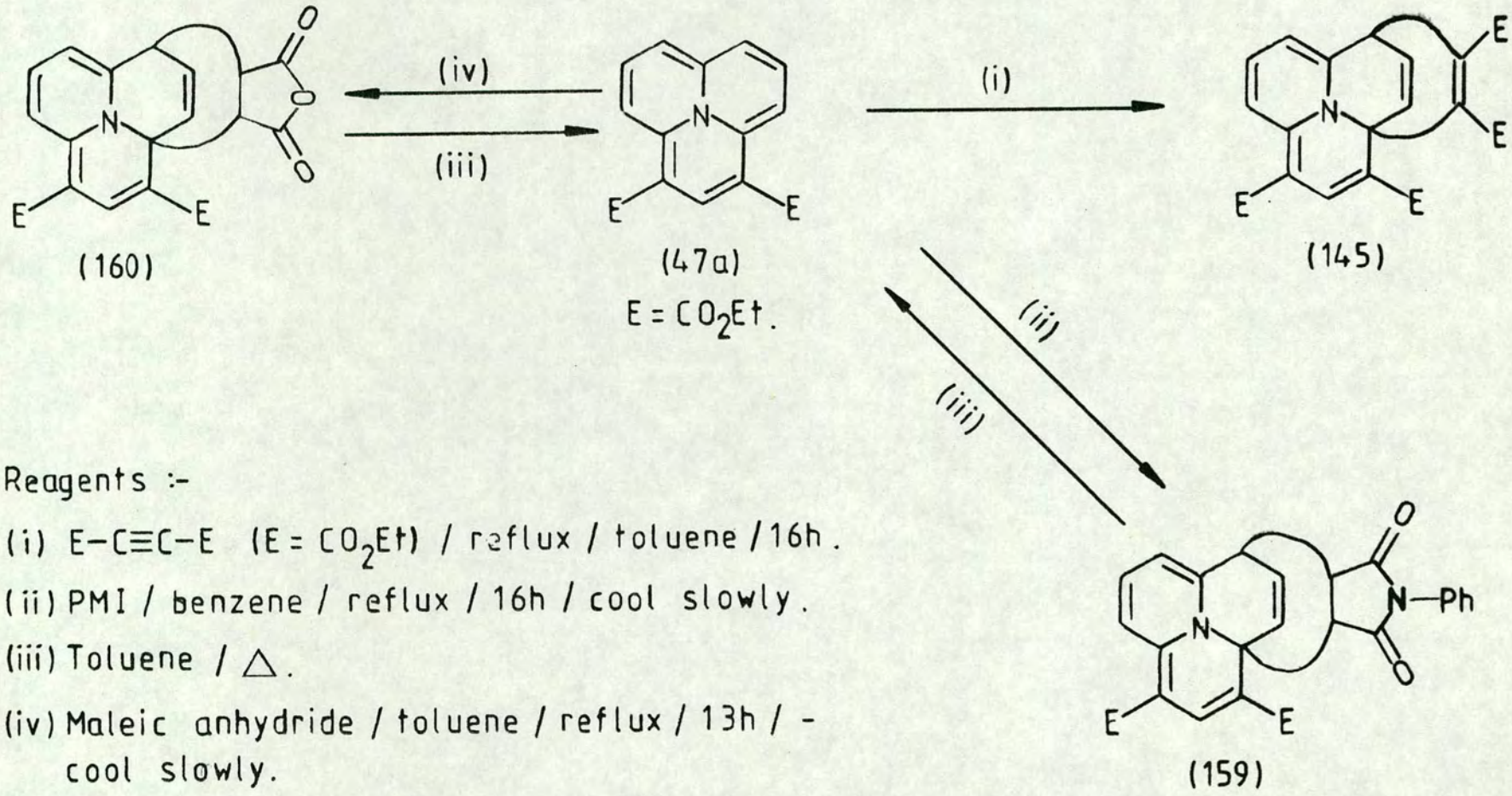
4.2 Reactions of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with potential cycloaddition reagents

4.2.1 Reactions with stable dienophiles: cycloadditions and substitutions

It is already known that [3.3.3]cyclazines can react as dienes in Diels-Alder cycloaddition reactions[22] (see scheme 10; Introduction) with such electron deficient acetylenes as dimethyl acetylenedicarboxylate (DMAD) to give etheno-bridged structures such as compound (63). It was found, during this present work, that the cyclazine diester (47a) undergoes similar reactions with other dienophiles, and also gives substitution products as an alternative to cycloaddition. In some cases both cyclo-addition and substitution reactions were shown to occur.

When an excess of diethyl acetylenedicarboxylate was refluxed with the cyclazine diester (47a) in toluene for sixteen hours, a red crystalline solid was isolated in 63% yield (scheme 26). This red adduct was identified as the expected etheno-bridged compound (145) by its characteristic spectroscopic details which were closely comparable to those of the known[22] adduct (63).

When this reaction was repeated in ethanol, the cycloadduct (145) was formed in only 16% yield, but three other products of higher chromatographic mobility were isolated by preparative t.l.c. and identified by a combination of mass spectrometry and proton n.m.r. (Table 11). These products, in order of decreasing R_f on t.l.c.



(160)

(47a)
E = CO_2Et.

(145)

(159)

Reagents :-

(i) E−C≡C−E (E = CO_2Et) / reflux / toluene / 16h.

(ii) PMI / benzene / reflux / 16h / cool slowly.

(iii) Toluene / △.

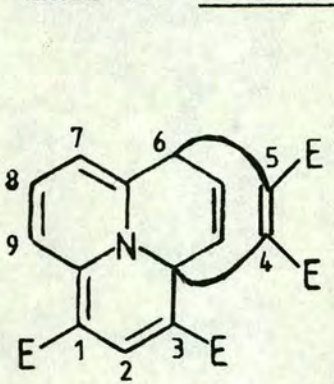
(iv) Maleic anhydride / toluene / reflux / 13h / - cool slowly.

Scheme 26.

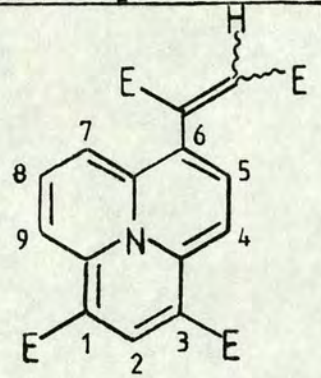
(silica) were shown to be two substitution products, (SR1; 6%) and (SR2; 6%) [m/z 481], and a product (SR3; 4%) [m/z 651] derived from one molecule of the cyclazine and two molecules of the acetylenic ester. The two monosubstituted products were red-purple solids (brown spot on t.l.c.), the structures of which were assigned on the basis of their ^{1}H n.m.r. spectra. In both compounds, one doublet of the AX spin system (ring B protons) was close to the H-8 triplet and this was assigned to H-5; the other doublet was close to the H-9 resonance in SR1 and close to the H-7 resonance in SR2. These doublets were therefore assigned to H-4 and H-6, respectively, thus identifying SR1 as the 6-substituted isomer (146) and SR2 as the 4-substituted isomer (147). In addition to the cyclazine and ethyl resonances, the n.m.r. spectrum of each isomer contained a singlet due to the olefinic proton of the substituent group. The chemical shift (δ 6.79) of this proton in SR1 showed that the double bond had the E-configuration [cf. dimethyl fumarate (δ 6.67); dimethyl maleate (δ 6.14)], but the corresponding chemical shift (δ 6.46) for SR2 was not sufficiently close to either of the reference values to allow a configurational assignment to be made.

The other isolated material, a red oil (SR3), was both a cycloadduct and a substitution product. The ^{1}H n.m.r. spectrum of this compound was very similar to that of the monocycloadduct (145) (Table 11) but the resonance due to H-7 was absent. The spectrum also showed signals due to two additional ethyl ester groups and an olefinic

Table 11. ^{1}H n.m.r. spectra of cycloadducts and substitution products (145-148)

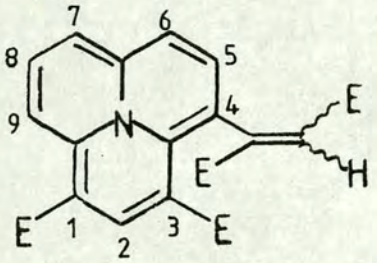


(145)

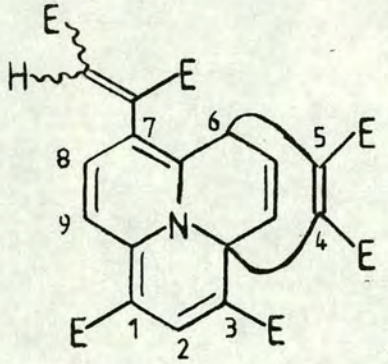


(146)

E = CO_2Et.



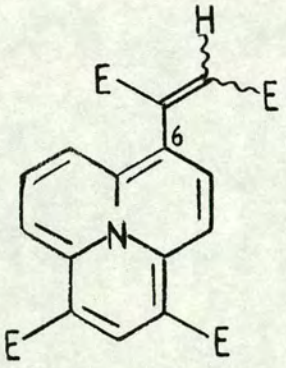
(147)



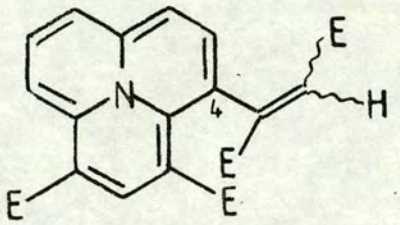
(148)

δ/H[a]	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	Other protons	Coupling constants J/Hz
(145) b)	[4.2,q] [1.3,t]	8.21 (s)	[4.2,q] [1.3,t] ⟷	[4.2,q] [1.3,t]	[4.2,q] [1.3,t]	4.99 (dd)	6.42 (dd)	7.06 (dd)	8.43 (dd)	6.78 (dd) 6.86 (dd)	$J_{7,8}$ 6,7; $J_{8,9}$ 9.2; $J_{7,9}$ 1.4 $J_{etheno-etheno'}$ 6.9 $J_{6,etheno}$ 5.9; $J_{6,etheno'}$ 2.1 Hz
(146) c)	[4.0-4.2,q] [1.2-1.4,t]	7.20 (s)	[4.0-4.2,q] [1.2-1.4,t]	6.76 (d)	5.93 (d)	[4.0-4.2,q] [1.2-1.4,t]	4.92 (dd)	6.13 (t)	6.80 (dd)	H-6'C=CHE 6.79 (s)	$J_{7,8}$ 8.2; $J_{8,9}$ 8.3; $J_{7,9}$ 1.5; $J_{4,5}$ 8.5 Hz
(147) c)	[3.8-4.5,q] [1.0-1.4,t]	7.26 (s)	[3.8-4.5,q] [1.0-1.4,t] ⟷		6.31 (d)	5.62 (d)	5.64 (dd)	6.48 (t)	7.13 (dd)	H-4'C=CHE 6.46 (s)	$J_{7,8}$ 8.2; $J_{8,9}$ 8.3; $J_{7,9}$ 1.6; $J_{5,6}$ 8.8 Hz
(148) c)	[4.0-4.4,q] [1.2-1.3,t]	8.21 (s)	[4.0-4.4,q] [1.2-1.3,t] ⟷			4.93 (dd)	[4.0-4.4,q] [1.2-1.3,t]	6.81 (d)	8.45 (d)	etheno 6.7-6.8 H-7'C=CHE 7.13 (s)	$J_{8,9}$ 9.4; $J_{6,etheno}$ 5.1, 2.9 Hz

a) Values in parenthesis refer to substituents. b) 200 MHz ($CDCl_3$) c) 80 MHz ($CDCl_3$)



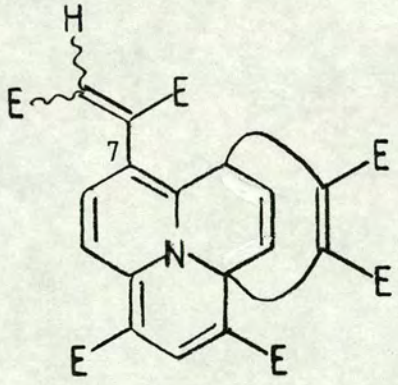
SR1
(146)



SR2
(147)

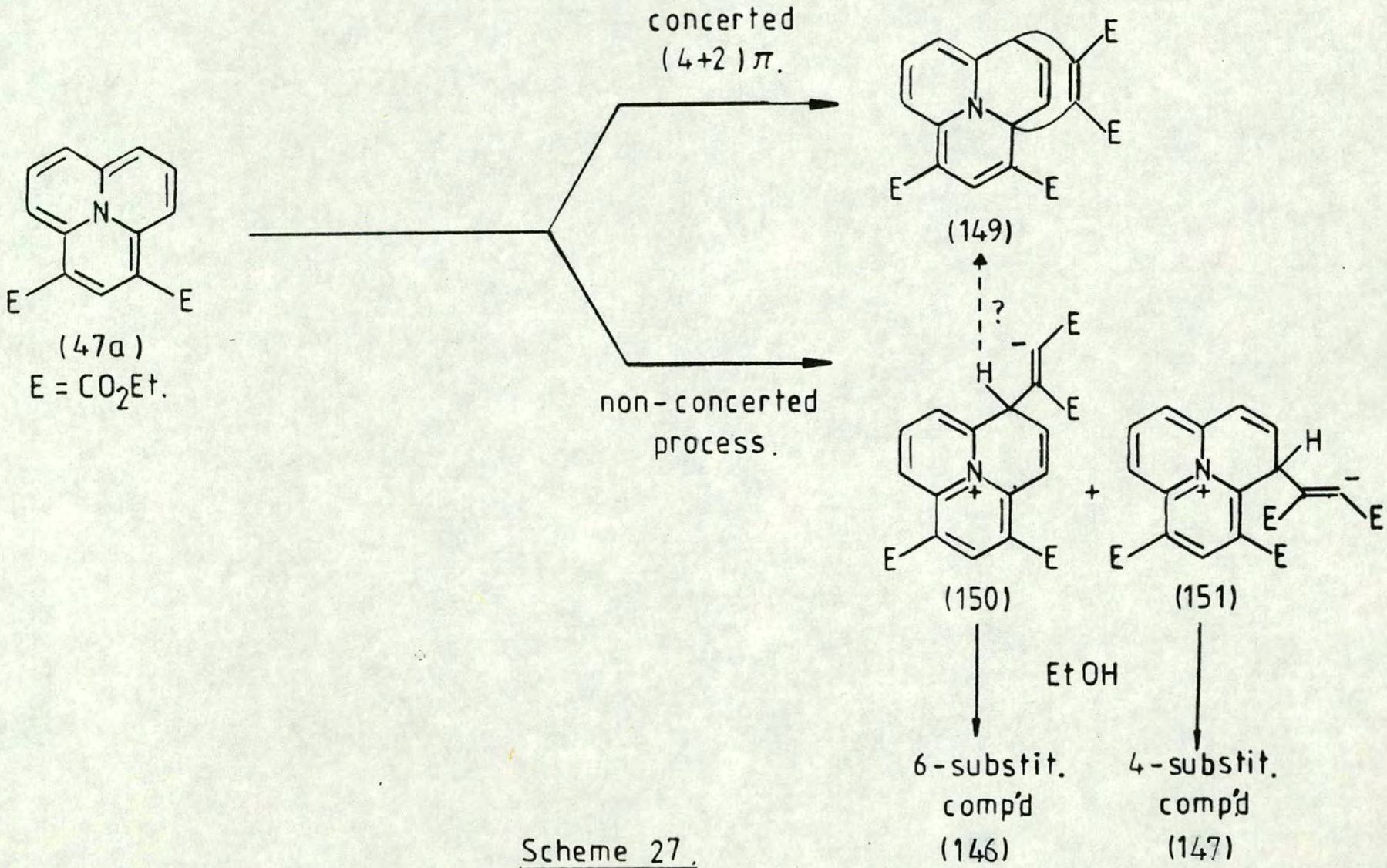
E = CO_2Et.

proton (singlet, δ7.13), indicating the presence of a fumarate substituent. Accordingly, the structure (148) was assigned to SR3, which is a 7-substituted cycloadduct.



SR3
(148) E = CO_2Et.

At this stage it is appropriate to consider the rôle of the solvent in influencing the course of this reaction (scheme 27). The use of the non-polar aprotic toluene as solvent is considered to favour a concerted (4+2)π cycloaddition to give the monocycloadduct (149). In ethanol, however, solvent polarity will favour the formation of intermediate dipolar ions [(150) and (151)]


concerted
(4+2)π.
(47a)
E = CO2Et.
(149)
non-concerted
process.
?
(150)
(151)
EtOH
6-substit.
comp'd
(146)
4-substit.
comp'd
(147)

Scheme 27.

which may either be converted into the two substitution products (152) and (153) via solvent-mediated proton-transfer reactions or, in the case of the 6-substituted intermediate (150), lead to a cycloadduct by a non-concerted mechanism. It is, of course, possible that the cycloadduct is formed, even in ethanol, by the concerted process and that only the substitution products are formed from the dipolar ions. It seems likely that the cycloaddition-substitution product (148) is formed by substitution followed by cycloaddition (rather than vice-versa) since the initial cyclazine π-system is probably more susceptible to electrophilic attack than the 4H-quinolizine π-system in the cycloadduct (149).

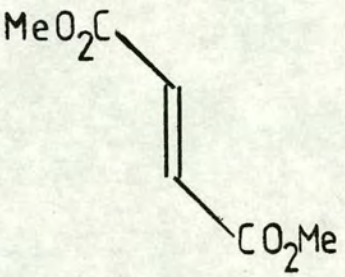
A similar solvent-dependent competition between cycloaddition [(8+2)π] and substitution has been observed[55] in the reactions of indolizines with dimethyl acetylene-dicarboxylate.

In view of the successful reaction of an acetylenic dienophile with the cyclazine diester (47a), a number of olefinic dienophiles were tried. However, the doubly activated acyclic dienophiles, dimethyl fumarate (154), dimethyl maleate (155)[§], and fumaronitrile (156) yielded no cycloadducts with the cyclazine diester even after several hours in refluxing benzene or toluene. In each

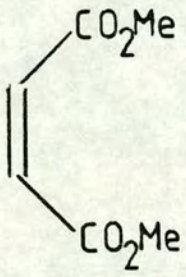
---

§ During the attempted reaction of the cyclazine with dimethyl maleate, a faint orange-red spot was visible by analytical t.l.c.. However, this was a trace amount only and no product was isolated.

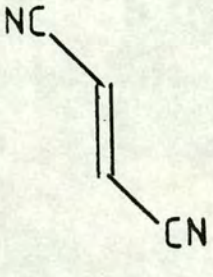
case, the starting material (47a) was recovered in 80-85% yield.



(154)

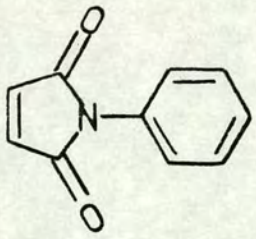


(155)

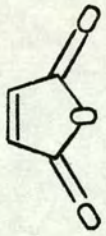


(156)

In expectation of greater reactivity, cyclic dienophiles were then tried including N-phenylmaleimide (157) [P.M.I.] and maleic anhydride (158). Both of these dienophiles gave rise to Diels-Alder adducts with the cyclazine diester (47a) as shown in scheme 26.



(157)



(158)

The N-phenylmaleimide adduct, (159), was formed in 20% yield by refluxing the cyclazine with PMI (157) in dry toluene and in 46% yield when benzene was used as the solvent, the benzene solution being allowed to cool slowly from reflux. This increased yield in a lower boiling solvent seemed surprising until it was noted that heating the PMI adduct (159) in toluene caused it to revert to the cyclazine starting material. The pink

t.l.c. spot corresponding to the cycloadduct (159) reappeared when the solution was cooled slowly but the cyclazine spot did not disappear completely. These observations are evidence of a temperature-dependent equilibrium between the cycloadduct (159) and the reactants and indicate that the cyclazine (47a) is of rather low reactivity as a dienic substrate in the Diels-Alder reaction.

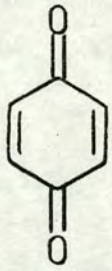
The PMI-cyclazine cycloadduct was a red solid that showed the general characteristics outlined earlier (section 4.1) for cycloadducts. Its 360 MHz ^{1}H n.m.r. spectrum (Table 12) was rich in detail, particularly in the regions (δ6.6 - 6.8 and 4.0 - 4.3) where lines due to the protons from the bridged ring system were interspersed with lines due to other structural features. The region near δ4.1 was further complicated by the occurrence of diastereotopicity in one of the ester CH_2 groups (at C-3). Despite these complexities, a complete assignment was possible and this was supported by selective decoupling experiments, as detailed in Table 12.(P252).

By using a procedure analogous to that for the PMI adduct, the cycloadduct (160) of the cyclazine diester (47a) with maleic anhydride (158) was isolated from the slowly cooled solution after reaction in toluene. This adduct was isolated as a slightly impure red solid which resisted attempts to recrystallise it by reverting to starting materials.

The proton n.m.r. spectrum of the maleic anhydride

adduct (160) was obtained from the slightly impure sample, but the same salient features as observed for the PMI adduct (159) were clearly visible (Table 13/Experimental section)[p253]. An attempt to obtain a mass spectrum of this unstable adduct (160) gave a large peak at m/z 311 which corresponds to the cyclazine starting material but no molecular ion peak corresponding to the intact adduct ($M^{+\cdot}$ 409) was observed.

Another potential cyclic dienophile for the formation of a cycloadduct was p-benzoquinone (161). However, when



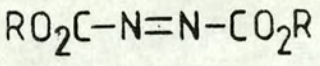
(161)

this compound was refluxed with the [3.3.3]cyclazine diester (47a) in toluene, no red cycloaddition product was observed by t.l.c., but numerous other products were formed in low yield and much dark material remained on the base-line. Although none of these products were isolated or characterised, it appeared that decomposition of the cyclazine starting material had occurred to a large extent. Quinones are known to be good electron-acceptors and it is possible that the reaction proceeds here by initial electron-transfer from cyclazine to quinone, rather than by cycloaddition. The resulting radical-cation might well

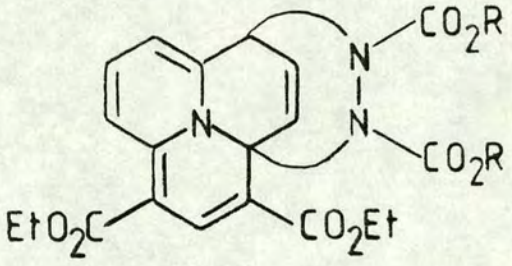
lead mainly to products of decomposition.

After the successful synthesis of (4+2)π cycloadducts using acetylenic and cyclic olefinic dienophiles, some reactions using dienophilic azo-compounds were undertaken.

The first experiment was carried out with diethyl azodicarboxylate[56,57] (162a) from which the cycloadduct (163a) might have been expected. However reaction of the



(162)

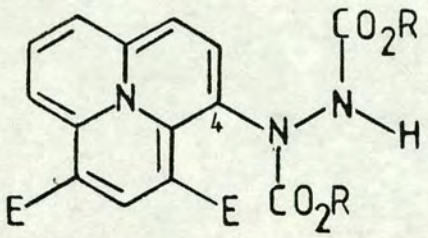


(163)

a). R = Et.
b). R = Bu^t.

azodiester with the cyclazine diester (47a) under mild conditions (THF at room temperature) gave a complex mixture of products which were difficult to separate and none of which was the characteristic red colour of the cycloadduct. By using a combination of column chromatography and preparative t.l.c. it was possible to isolate the major component of the mixture as a dark brownish-green solid, the mass spectrum of which showed a molecular ion at m/z 485, corresponding to a 1:1 adduct of the reactants. Infrared spectroscopy revealed the presence of an NH stretching band ($\bar{\nu}_{max}$ 3480 cm^{-1}) and also carbonyl bands for the ester and amide groups at $\bar{\nu}_{max}$ 1745, 1720. 1685 and

1620 cm^{-1}. The proton n.m.r. spectrum of this product in deuteriochloroform showed considerable line-broadening [even after the solution had been shaken with sodium dithionite (in D_2O) to remove paramagnetic impurities] and appeared to contain too many lines but its general form was of the type expected from a monosubstitution product of (47a). In the region of the spectrum corresponding to unsaturated CH there were three multiplets, at δ5.4 - 5.5, 6.3 - 6.5 and 6.9 - 7.1, each accounting for two of the remaining cyclazine protons and matching the chemical shifts of H-6 and 7, H-5 and 8, and H-2 and 9, respectively, of the 4-substitution product (164a) obtained in the reaction with diethyl acetylenedicarboxylate. Accordingly the structure (164a) was assigned to this product. The line-broadening



(164)

E = CO_2Et.

a). R = Et.

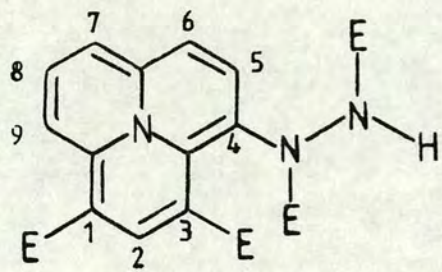
b). R = Bu^t.

and apparently excessive multiplicity were thought to be caused by restricted rotation about the amide (urethane) bonds and the consequent presence of two or more configurational isomers. Similar effects in the n.m.r. spectrum of other di(alkoxycarbonyl)hydrazines have been

reported[58]. When the n.m.r. spectrum was run in d^6-dmso at high temperature (+100°C), these effects of restricted rotation were eliminated and a normal well-resolved pattern of lines was obtained, fully consistent with structure (164a). Thus the spectrum showed (i) an AB-system (δ5.88 and 6.48) for the H-5 and H-6 resonances, (ii) an AXY system (δ5.86, 6.65 and 6.91) for the H-7, 8 and 9 protons, and (iii) a singlet (δ7.02) for H-2. A broad one-proton singlet at δ7.90, removed by addition of D_2O, was assigned to the NH proton [Table 14]. Decreasing the temperature over the range +100° to +26°C caused a reappearance of line-broadening and, after passage through regions of coalescence, to an increase in multiplicity.

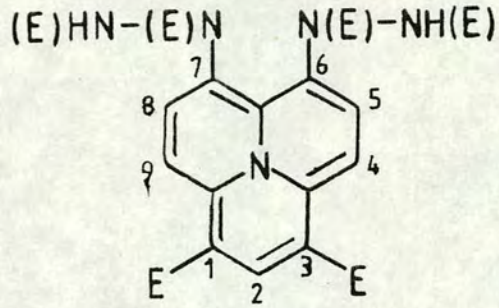
Also isolated, in lower yield, from the complex reaction mixture was another greenish-brown solid, the mass spectrum of which showed a molecular ion at m/Z 659, corresponding to a 1:2 cyclazine-azodicarboxylate adduct. This solid once again gave a line-broadened n.m.r. spectrum in $CDCl_3$ (even with a dithionite shake) from which no structural conclusions could be drawn. In d^6-dmso at 108°C, however, the ^1H n.m.r. spectrum revealed a symmetrical structure, showing a one-proton singlet at δ7.33 (H-2) and two two-proton doublets (AX) at δ6.25 and 6.90 (^3J = 9.0 Hz) attributable to H-5 and 8 and to H-4 and 9, respectively [Table 14]. Also present were a broad two-proton singlet at δ8.08 (NH; removed by adding D_2O) and signals corresponding to four ethyl ester groups. Infrared spectroscopy showed the presence of both NH and

Table 14. [200 MHz] ^{1}H n.m.r. spectra of compounds (164a) and (164c) in d^6-dmso



(164a)

E = CO_2Et.

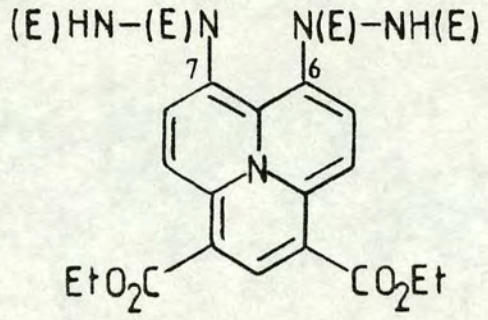


(164c)

δ_H (d^6-dmso)[a]	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	Coupling constants
(164a)[b]	1.1-1.3 (t) 3.9-4.2 (q)	7.02 (s)	1.1-1.3 (t) 3.9-4.2 (q) (7.90 br.s[d])		6.48 (d)	5.88 (d)	5.86 (dd)	6.65 (t)	6.91 (dd)	$J_{5,6}$ 9.2 Hz $J_{7,8}$ 8.1 $J_{8,9}$ 8.3 $J_{7,9}$ 1.5
(164c)[c]	1.17 (t) 4.04 (q)	7.33 (s)	1.17 (t) 4.04 (q)	6.90 (d)	6.25 (d)	1.22 (t), 4.13 (q), 8.08[d] (br s)		6.25 (d)	6.90 (d)	$J_{4,5}$ 9.0 Hz

a) Values in parenthesis are for substituent groups
b) Spectrum run at 373 K. Resolution decreases at lower temps.
c) Spectrum run at 381 K. Resolution decreases at lower temps.
d) Peak removed on shaking the sample with D_2O, [NH].

carbonyl (ester and azodiester) bands [see experimental section]. Thus the spectroscopic evidence showed that this was a 6,7-disubstituted cyclazine derivative (164c). Had the substituents been in positions 4 and 9, the high



(164c)

E = CO_2Et

frequency doublet (δ6.90) would have been absent and a low frequency doublet (ca. δ5.9) due to H-6 and 7 would have been present instead.

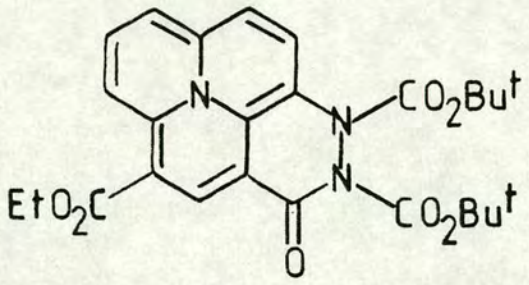
It was interesting to note that both of the above compounds isolated from the reaction of the cyclazine diester with diethyl azodicarboxylate were substitution products rather than cycloadducts. Possibly, other mono- and di-substituted compounds were present in the product mixture but these were not isolated.

In the hope of obtaining a less complex mixture of products, the foregoing experiment was repeated using di-t-butyl azodicarboxylate[59] (162b) which, owing to steric factors, was expected to be less reactive than diethyl azodicarboxylate. However, once again a complex mixture of reaction products was found, and again there

were difficulties in separating the components.

The major component was a mono-substitution product (M^+ 541), isolated as a dark brownish-green solid. Infrared and proton n.m.r. spectroscopy showed that this product was analagous to that, (164a), obtained from diethyl azodicarboxylate and the structure (164b) was assigned to it. Line-broadening and excessive multiplicity were again apparent in the n.m.r. spectrum which showed more than the required number of peaks in the t-butoxy region as well as in the unsaturated CH region.

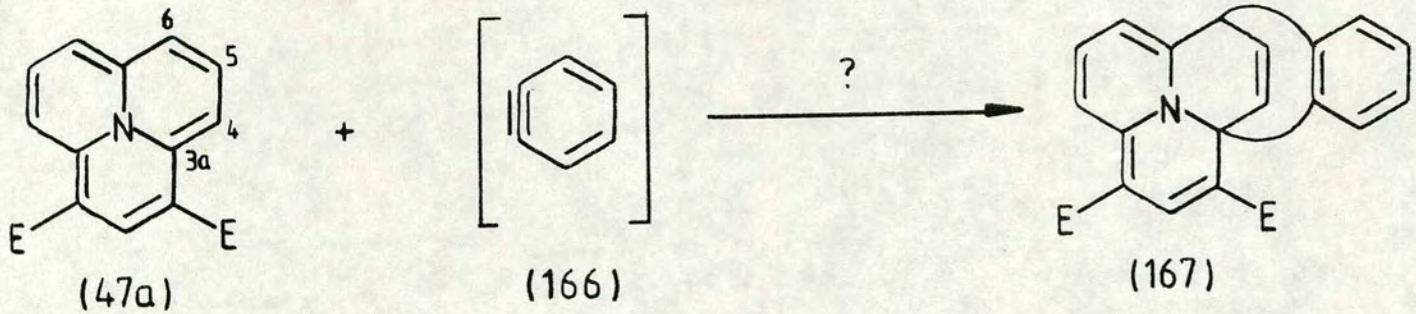
A second, minor product of the di-t-butyl azodicarboxylate reaction, was isolated as a pale brown solid, the mass spectrum of which showed a molecular ion at m/Z 495, corresponding to [(47a) + $N_2(CO_2Bu^t)_2$ - EtOH]. Its infrared spectrum showed the presence of ester and amide carbonyl groups ($\bar{\nu}_{max}$ 1760, 1725, 1690 and 1655 cm^{-1}), but no NH group. The proton n.m.r. spectrum, which was not line-broadened, showed an AMX system [δ5.66 (H-7), 6.37 (H-8) and 7.02 (H-9)], an AX system (δ5.46 and 6.57) and a singlet (H-2) at δ7.32. The fact that the AX chemical shifts were close to those of H-7 and 8, rather than to H-8 and 9, showed that H-4 was absent. The ester resonances revealed the presence of two t-butoxycarbonyl groups but only one ethoxycarbonyl group. Thus the structure (165) was assigned to this product which had presumably been formed from (164b) by intramolecular amide formation.



(165)

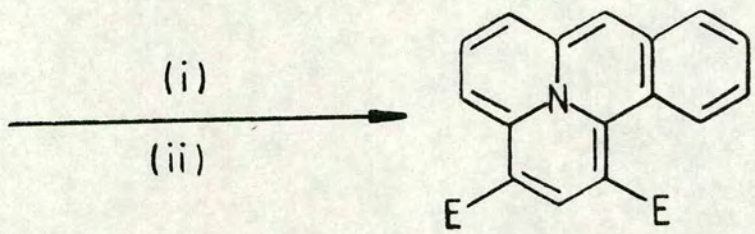
4.2.2 Reaction of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with benzyne

Benzyne is well known to be a reactive dienophile but, unlike the dienophiles used for the work described in section 4.2.1, it is a short-lived intermediate rather than a stable compound. The cycloaddition of benzyne to [3.3.3]cyclazines was of particular interest because of the possibility that such a reaction might provide a starting point for the synthesis of benzo[3.3.3]cyclazines as outlined in Scheme 28. It was thought that benzyne would react, as had the previous dienophiles, across the 3a,6- positions of the cyclazine diester (47a) to give the etheno-bridged adduct (167). Subsequent hydrogenation and extrusion of ethylene (see Introduction - section 3.3.1) could then give the required benzo-derivative (168). Molecules of this type, containing an aromatic ring system fused to an antiaromatic ring system, have not been well studied but the effect of one ring system upon the properties of the other is of considerable theoretical interest.



(47a) (166) (167)

E = CO_2Et



(168)

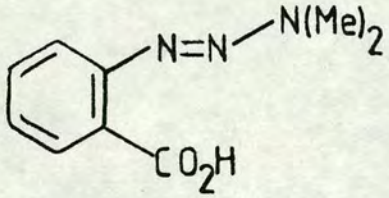
Reagents :-

(i) H_2 /catalyst.

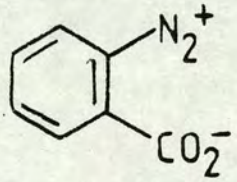
(ii) $\triangle$ / [$-C_2H_4$].

Scheme 28.

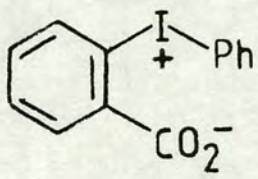
Although benzyne (166) may be generated by a variety of methods, often involving the use of strong bases, the thermal decomposition of a single precursor was considered to provide the least opportunity for side reaction to occur. One such approach to benzyne is that of Simamura[60] and his co-workers which utilises the dimethyltriazeno-benzoic acid (169) as the precursor. Heating this compound in chlorobenzene (135°C) generates benzyne (166) by controlled decomposition of the triazene, presumably via the diazonium betaine (170) which, though dangerously explosive, has itself been used as a source of benzyne. When this procedure was carried out in the presence of the cyclazine diester (47a), multiple product formation occurred, but a major part of the cyclazine remained after 15 hours. More of the precursor (0.5 equiv.) was added and heating was continued for 9 hours, after which an attempt to isolate the products by preparative t.l.c. gave only very small amounts of red solids. These products



(169)



(170)



(171)

were not obtained sufficiently pure for characterisation purposes, being of generally low stability and prone to decomposition. About 50% of the starting cyclazine (47a)

was recovered in an impure state. No further work was performed on this approach.

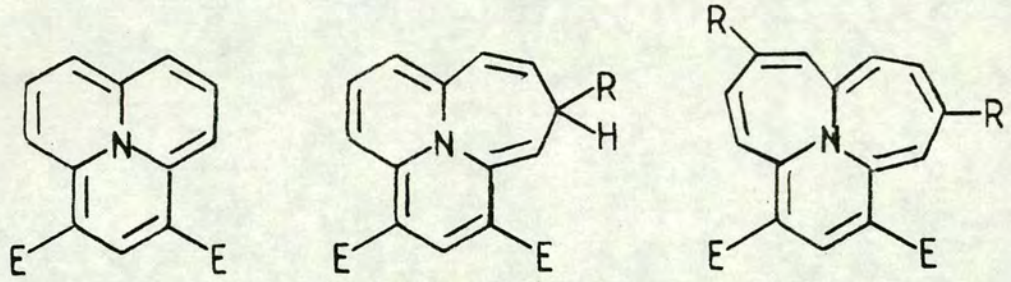
Another approach to the thermal generation of benzyne is that of Beringer and Huang[61] who used 2-phenyliodoniobenzoate (171) as the precursor. However, when this compound and the cyclazine diester (47a) were refluxed together in γ-butyrolactone (205°C), extensive decomposition was soon evident (0.5 h). T.l.c. then revealed the presence of more than seven products together with some cyclazine starting material. No work-up was attempted since only trace amounts of the orange, pink and yellow products were present.

It is interesting to note that in both of these benzyne reactions, the starting material (47a) was still present at the work-up stage, despite, in one case, the use of an excess of the benzyne precursor. Thus, it seems likely that the dienic reactivity of the cyclazine nucleus is insufficient to allow efficient trapping of such a short-lived intermediate as benzyne. Evidence of low reactivity was also obtained in the cycloaddition reactions with stable reactive dienophiles, (section 4.2.1) where typically the cyclazine and the dienophile were refluxed together for 16 hours before substantial product formation was achieved.

4.2.3 Reaction of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with ethoxycarbonylcarbene.

Ethyl diazoacetate (N_2CHCO_2Et) and diazomethane have frequently been used[62] as carbene precursors for the ring

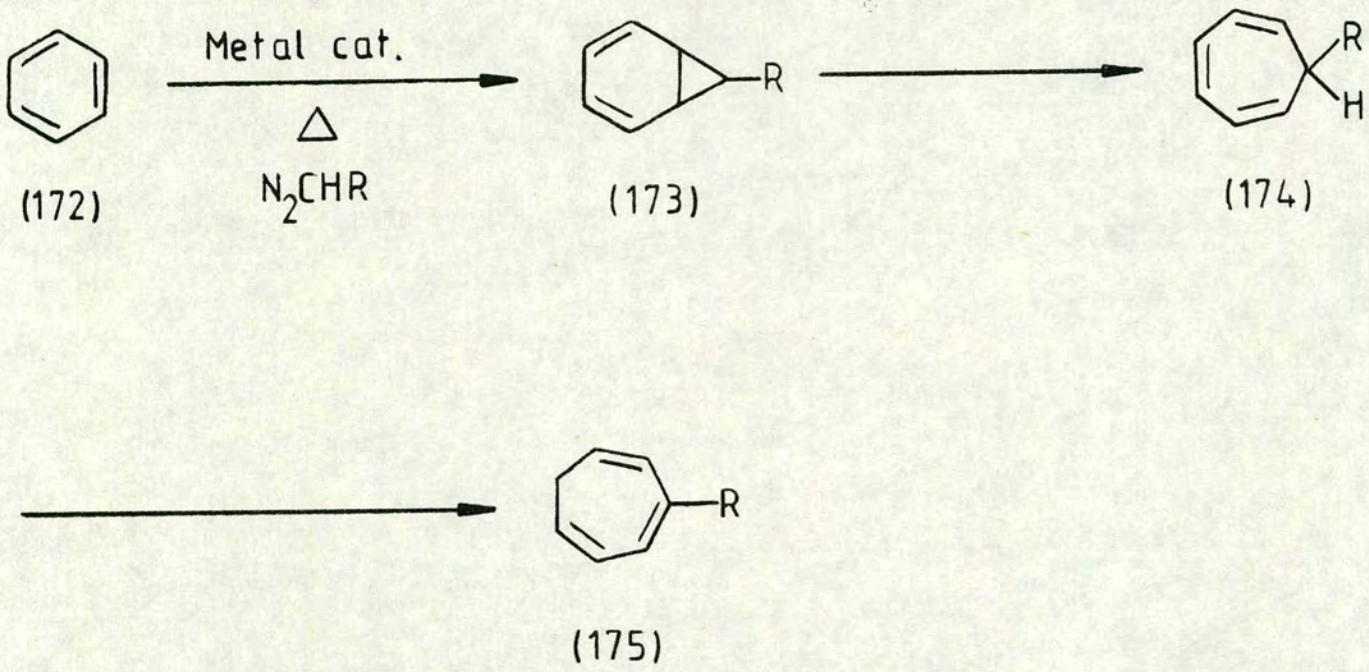
expansion of benzenoid compounds to cycloheptatriene derivatives (scheme 29). Typically, a transition[63] metal or metal complex is used to catalyse the decomposition of the diazo-compound and the resulting carbene (or "carbenoid" species) reacts, by cycloaddition, with an aromatic bond. The intermediate norcaradiene (173) is normally short-lived and undergoes electrocyclic isomerisation to a cycloheptatriene. A similar ring expansion of the [3.3.3]cyclazine (47a) could, in principle give a [3.3.4]cyclazine (e.g. 176) and might possibly proceed further to a [3.4.4]cyclazine, the fully unsaturated form (177) of which contains a 14π-electron



(47a) (176) (177)

for E = CO_2Et.

periphery. Neither of these ring systems has yet been synthesised. In testing these ideas, the reagent employed as the carbene precursor was ethyl diazoacetate (EDA) in the presence of rhodium(II) acetate which, for many applications, has been shown[63,64] to be the most efficient catalyst for the decomposition of diazo-compounds.



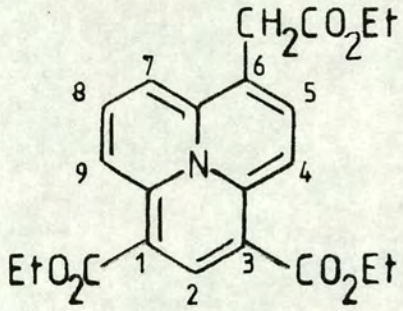
(172) (173) (174) (175)

Scheme 29.

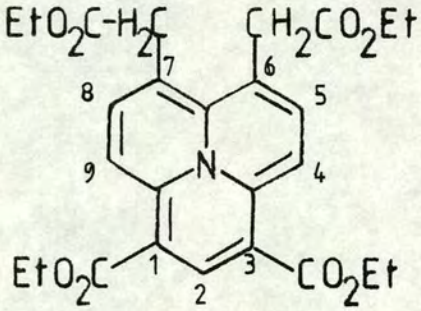
In order to minimise the reaction of ethoxycarbonylcarbene with its own precursor, the diazoester was added very slowly by motor-driven syringe to a dilute refluxing solution of the cyclazine diester (47a) in dichloromethane in the presence of a catalytic amount of rhodium(II) acetate [$Rh_2(OAc)_4$]. This reaction gave a complex mixture of products which proved difficult to separate. However, two products, C1 and C2, were isolated in low yield by a combination of preparative t.l.c. (silica) and dry flash column chromatography. The first (higher Rf) of these products was an orange solid, the proton n.m.r. spectrum of which revealed (Table 15) the presence of two components, C1A and C1B. These were incompletely separable, even by h.p.l.c., but their respective proton n.m.r. spectra were identifiable by grouping together those resonances that showed integral intensity relationships to one another. The major component (C1A) showed a two-spin (AX) system (δ 6.10 and 6.70, ^3J = 8.4 Hz), a three-spin (AXY) system (δ 5.22, 6.23 and 6.84, ^3J = 8.4 Hz; ^4J = 1.4 Hz) and a singlet at δ7.17, this pattern giving a clear indication that the compound was a 6-substituted derivative of (47a). In addition, ethyl ester resonances and a two-proton singlet at δ2.72 were indicative of a CH_2CO_2Et substituent. Thus the structure (178) was assigned to C1A.

The minor component (C1B) of the orange solid had a more simple n.m.r. spectrum [Table 15] showing two

Table 15. 200 MHz ^{1}H n.m.r. data for the substitution products (178) and (179)



(178)

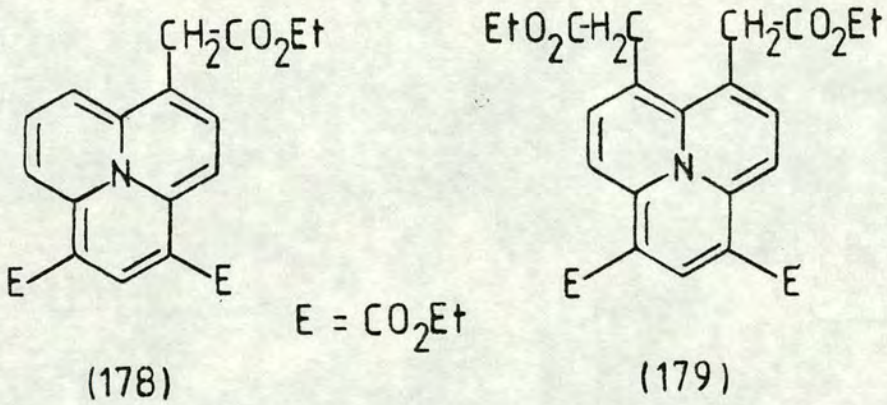


(179)

$\delta_H(CDCl_3)$ [a] /H	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	Coupling constants J/Hz
(178)	4.0-4.2 (q) 1.2-1.3 (t)	7.17 (s)	4.0-4.2 (q) 1.2-1.3 (t)	6.70 (d)	6.10 (d)	2.72 (s/CH_2) 4.0-4.2 (q) 1.2-1.3 (t)	5.22 (dd)	6.23 (t)	6.84 (dd)	$J_{4,5}$ 8.4; $J_{7,8}$ 8.4; $J_{8,9}$ 8.4; $J_{7,9}$ 1.4 Hz J_{vic} 7.1 Hz
(179)	4.0-4.2 (q) 1.2-1.3 (t)	7.29 (s)	4.0-4.2 (q) 1.2-1.3 (t)	6.90 (d)	6.22 (d)	3.03 ($s/2 \times CH_2$) 4.0-4.2 (q) 1.2-1.3 (t)		6.22 (d)	6.90 (d)	$J_{4,5}$ 8.6 Hz J_{vic} 7.1 Hz

a) Values in parenthesis indicate the resonance value of the substituent group

doublets (δ 6.22 and 6.90, ^3J = 8.6 Hz), each equivalent to two protons and two singlets, one at δ7.29, corresponding to the H-2 ring proton, and the other, equivalent to four protons, at δ3.03. The symmetrically disubstituted structure (179) was therefore assigned to C1B and, from the intensity relationships of various peaks in the combined n.m.r. spectrum, the ratio of C1A:C1B was calculated as approximately 3:1.

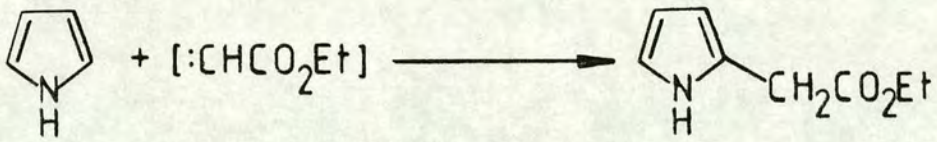


(178) (179)

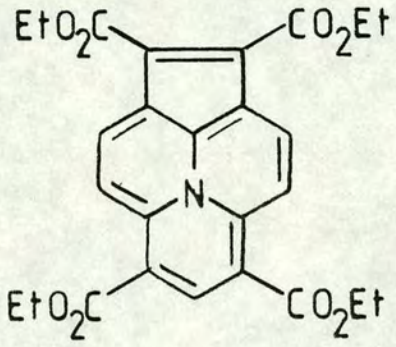
Further evidence in support of the structures assigned to C1A and C1B was obtained from the mass spectrum of the mixture (C1) which showed peaks at the expected m/z values (397 and 483) for the molecular ions of (178) and (179). Accurate mass measurements confirmed the molecular formulae. The u.v.-visible absorption spectrum of C1, being closely similar to that of the starting material (47a), was also consistent with these structures.

The formation of substitution products rather than ring-expansion products is also commonly observed[65] when

other electron-rich heterocycles such as pyrroles and indoles react with ethoxycarbonylcarbene eg.



The other component (C2) isolated from the reaction mixture was a red solid, the mass spectrum of which showed a molecular ion at m|z 479, corresponding to [(47a) + $2CHCO_2Et$ - 4H]. The proton n.m.r. spectrum of C2 was remarkably simple with two two-proton doublets [i.e. two superimposed AB systems] at δ8.57 and 8.70 (^3J = 9.2 Hz), and a sharp one-proton singlet at δ8.89. The ethyl resonances (triplets and quartets) showed that two pairs of ester groups were present (from integral values) in two slightly different environments. The simplicity of the spectrum showed that the symmetry of the starting material (47a) had been retained in this product and the high chemical shift values suggested that the ring system had become diatropic in character. The structure that best fits the data for C2 is (180) based on the cyclopenta[cd][3.3.3]cyclazine skeleton. Previous work[21] (see introduction; section 3.1) has shown that cyclopent-[cd]annelation in [3.3.3]cyclazine causes a change from paratropicity to diatropicity, in keeping with the observed n.m.r. data for C2.



(180)

The cyclopenta[3.3.3]cyclazine derivative (180) could perhaps have been formed from the 6,7-disubstituted cyclazine [(179) = C1B] by a process of dehydrogenative coupling of the substituent groups. However, another possibility is that the compound could have been formed by a reaction of the starting material (47a) with diethyl maleate or diethyl fumarate under the influence of the rhodium catalyst. These two unsaturated esters are known products from the decomposition of ethyl diazoacetate and are generally believed to be formed by reaction of ethoxycarbonylcarbene with the diazoester. In order to test this possibility, the cyclazine derivative (47a) was refluxed with diethyl fumarate in dichloromethane in the presence of rhodium(II) acetate, but none of the red product (C2) was observed.

In conclusion, it should be stated that although there was no evidence for the formation of [3.3.4]- or [3.4.4]cyclazine derivatives, the reaction of the [3.3.3]cyclazine (47a) with ethoxycarbonylcarbene gave

a number of uncharacterised products in addition to those described above. It is not possible, therefore, to exclude the possibility that these ring-expanded systems were formed to a minor extent.

4.3 Oxidation reactions of a [3.3.3]cyclazine derivative

4.3.1 Oxidation of a [3.3.3]cyclazine derivative - Formation of cyclazinones

As mentioned previously in the introduction, [3.3.3]cyclazines can be readily oxidised to radical cations which, particularly in the case of the 1,3-di-(ethoxycarbonyl) derivative (47a), may react further to give other characterisable products.

In the present work and in previous work performed in these laboratories[43], it was noted that the spot corresponding to 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine (47a), when exposed to air on a silica or alumina t.l.c. plate, gave rise to other products. When the t.l.c. plate was redeveloped these products were visible as a yellow and a fluorescent yellow-green spot, of lower chromatographic mobility relative to the cyclazine. It was also interesting to note that Leupin et al when studying[27b] the picosecond fluorescence from [3.3.3]cyclazine (3), reported emission from products of oxidative degradation. Their evidence indicated that two or more fluorescent species were being formed, but they failed to isolate any characterisable products, reporting only the recovery of intractable tars.

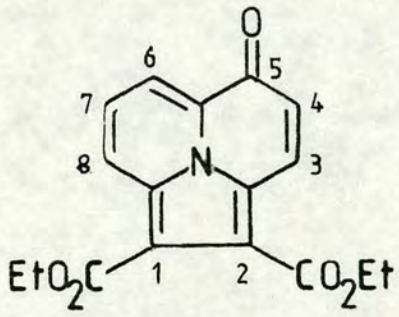
In the present work, initial oxidation reactions using 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine (47a) on silica preparative t.l.c. plates, exposed to air and light for eleven days, gave only small amounts of an orange solid

(fluorescent yellow-green on t.l.c.) [10%] and an orange-yellow solid (yellow spot on t.l.c.) [6%]. Mass spectrometry revealed that both these isolated products gave a parent ion (M^+) at m|z 313. In some experiments it was shown that these products also arise when the t.l.c. plate (silica or alumina) with the cyclazine spot is kept in the dark, thus implying that light is not necessary for the reaction. Also observed in these latter experiments was the presence of two red or pink products of even lower chromatographic mobility.

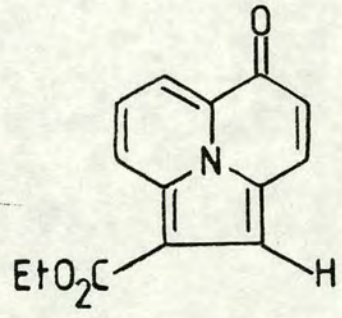
In order to obtain larger quantities of these oxidation products for identification purposes, a solution of the cyclazine diester (47a) in THF was kept in the presence of air and light until, after 48 hours, the t.l.c. spot corresponding to the starting material had disappeared. However, work-up by preparative t.l.c. revealed that the yield of fluorescent products was low and this was not significantly improved when the solution was stirred and refluxed with silica. Isolation by chromatography followed by purification by vacuum sublimation gave the two fluorescent yellow solids but the red products were not obtained in sufficient quantity for identification.

The fluorescent yellow band of higher Rf value on the t.l.c. (silica) gave an orange solid designated Y1, that was also highly fluorescent in solution (CH_2Cl_2, Et_2O, EtOAc, etc.). The proton n.m.r. spectrum of this material showed a three-spin system (AMX) at δ7.92, 8.55 and 8.85 p.p.m. (^3J = 8.5 and 7.7; ^4J = 1.1 Hz) and a two-spin

system (AX) at δ7.13 and 8.27 (^3J = 10.0 Hz). The singlet due to H-2 of compound (47a) was absent, but the two ester groups were still present. Mass spectroscopy showed a parent ion at m|z 313 with fragment peaks at m|z 240 and 168 due to the loss of the ester groups and at m|z 140 due to the subsequent loss of CO. These spectroscopic details, used in conjunction with the fact that the infra-red spectrum showed the presence of carbonyl groups at 1705 cm^{-1} (ester C=O) and 1647 cm^{-1} (strongly polarised C=O) suggested the 5H-[2.3.3]cyclazin-5-one structure (181) for Y1. The proton n.m.r. spectrum [Table 16] was in excellent agreement with that previously reported[6] for the 1-monoethoxycarbonyl derivative (182).



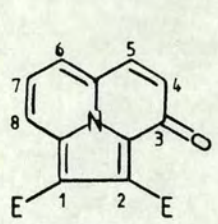
(181)



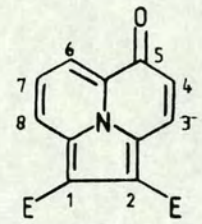
(182)

The other yellow product, Y2, isolated from these oxidation reactions was identified as an isomer of Y1 (181), and was shown to be the 3H-[2.3.3]cyclazin-3-one (183). This latter compound showed a three-spin (AXY) at δ8.76, 7.81 and 7.80 p.p.m., and a two-spin system (AX) at δ7.91 and 7.29 (^3J = 9.9 Hz) in the proton n.m.r. spectrum

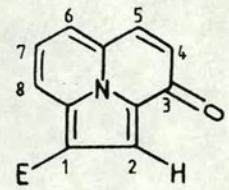
Table 16. ^{1}H n.m.r. spectra of compounds (33a), (181), (182) and (183)



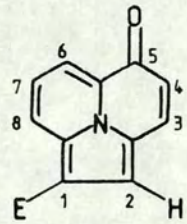
(183)



(181)



(33a)



(182)

E = CO_2Et

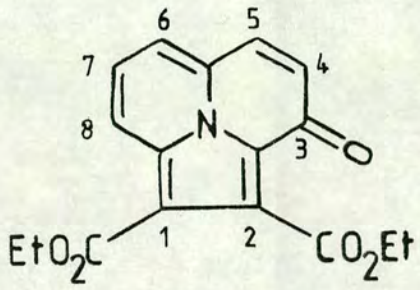
δ/H[a)b)]	H-1	2	3	4	5	6	7	8	Coupling J/Hz
(183)[c)]	[1.47 4.58]	[1.42 4.44]	-	7.29(d)	7.91(d)	7.80(dd)	7.81(dd)	8.76(dd)	$J_{4,5}$ 9.9 $J_{6,7}$ indet. $J_{7,8}$ indet. e) $J_{6,8}$ indet. J_{gem} 7.1
(181)[c)]	[1.44 4.47]	[1.46 4.57]	8.26(d)	7.12(d)	-	8.56(dd)	7.94(dd)	8.84(dd)	$J_{3,4}$ 10.0 $J_{6,7}$ 7.6 $J_{7,8}$ 8.6 $J_{6,8}$ 1.1 J_{gem} 7.1
(33a)[c)]	[1.45 4.45]	8.47(s)	-	7.36(d)	7.94(d)	7.8	7.8	8.78(dd)	$J_{4,5}$ 9.9 $J_{6,7}$ indet. $J_{7,8}$ indet. e) $J_{6,8}$ indet. J_{gem} 7.1
(182)[d)]	[1.46 4.47]	7.98(s)	8.08(d)	7.08(d)	-	8.56(dd)	7.92(t)	8.87(dd)	$J_{3,4}$ 9.8 $J_{6,7}$ 7.6 $J_{7,8}$ 8.4 $J_{6,8}$ 1.2 J_{gem} 7.1

a In $CDCl_3$ b Values in parenthesis indicate substituent shift

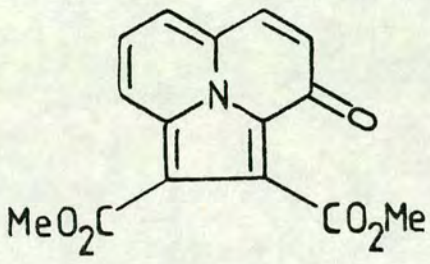
c At 200MHz d At 80 MHz

e 2nd order effects

(Table 16). These values are directly comparable with the previously reported[6] spectrum of (33b), the dimethoxycarbonyl equivalent of (183). The mass spectrum of Y2 (183) showed



(183)



(33b)

the parent ion peak at m|z 313 as expected, and the infrared spectrum showed two types of carbonyl peaks at 1735/1700 and 1610 cm^{-1}. Thus, the evidence points to the 3H-[2.3.3]cyclazin-3-one derivative (183).

To summarise, the two yellow products, Y1 and Y2, isolated from these oxidation reactions were recognised as the 1,2-di(ethoxycarbonyl)-3H- and 5H-[2.3.3]cyclazin--3- and -5-ones, (183) and (181) from their spectroscopic data. Identification was then confirmed by comparison with authentic specimens synthesised independently by unambiguous routes (Section 6). The formation of these [2.3.3]cyclazinones was also noted in reactions of the cyclazine diester (47a) with other oxidants as will be discussed.

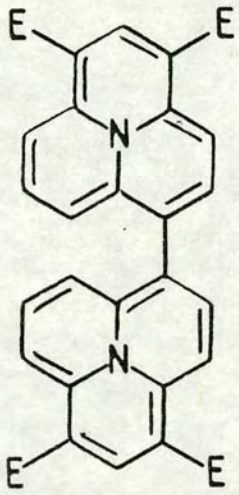
It was initially thought possible that these oxidation products (181) and (183) might have been formed by reaction of the cyclazine with singlet oxygen which

could be generated by energy transfer to ground state O_2 from a photo-excited triplet state of the cyclazine derivative (47a). One way of checking this possibility was to generate singlet oxygen chemically using the triphenylphosphite ozonide [$(PhO)_3PO_3$] method. Bartlett and his co-workers[66] recently published a procedure whereby singlet oxygen can be generated from the ozonide at low temperature (-78°C) and allowed to react with a substrate in situ. Under Bartlett's conditions, the [3.3.3]cyclazine diester (47a), gave the same oxidation products (181) and (183), but only in low yield. Also isolated by preparative t.l.c. was a red oil of low chromatographic mobility (silica), the mass spectrum of which showed a molecular ion (M^+) at m|z 341. However, this product was not obtained sufficiently pure for identification at this stage.

In view of the low yields in this experiment, the results could not be taken as evidence of any specific involvement of singlet oxygen in the oxidation process.

With a view to improving the efficiency of the oxidation reaction, and/or gaining insight into its mechanism, several other oxidising reagents of varied chemical types were investigated for their effects on the [3.3.3]cyclazine diester (47a). Almost all of these reagents gave rise to at least traces of the two [2.3.3]cyclazinones (181) and (183) isolated previously, and also to the two red products (now designated R1 and R2 in order of decreasing Rf value). In addition, some of

these oxidising reagents gave rise to significant amounts of the 6,6'-bicyclazinyl compound (74) which had been reported previously by Leaver and his co-workers[22] (Section 2/Introduction).



(74)

E = CO_2Et.

These oxidation experiments are described in detail in the experimental section and summarised in Table 17.

Although none of these reagents gave good yields of the yellow and red oxidation products, it became obvious that the formation of these products must be unrelated to the specific chemical nature of the oxidant. At this stage, therefore, it began to seem likely that all oxidants must act, at least initially, in the same way, namely by an electron abstraction to form a cyclazine radical cation. In common with many other examples of radical cations, this species might be in equilibrium with a small concentration of the cyclazine dication which could then react further with an oxygen nucleophile such as water or an oxyanion.

Table 17. Action of oxidants on 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine

Reagent	Conditions	Products observed or obtained (by prep. t.l.c. or flash chromatography) 6,6'- (74)	3- (183)	5-(181)	R1	R2	Other
10% Pd-C	THF/reflux/air	-	Trace	Trace	Trace	Trace	-
Ag_2O	THF/reflux	15%[a]	Trace	Trace	Trace	Trace	S.M. (27%)
Bu_4NIO_4[b]	CH_2Cl_2/stir/r.t.	57%[a]	Trace	Trace	Trace	Trace	S.M. (10%)
"	aqs.THF/stir/r.t.	10%	Trace	Trace	Trace	Trace	S.M. (Trace)
$(C_5H_5NH)_2Cr_2O_7$[c]	CH_2Cl_2/stir/r.t.	63%[a]	-	-	-	-	S.M. (30%)
NaOCl	CH_2Cl_2/H_2O/TEBA[d] stir/r.t.	5%	3%		<1%[e]	Trace	-
CrO_3	ACOH/r.t.	-	8%	15%	4%[e]	N.I.	g)
H_2O_2	aq. THF/$MnCl_2$/ stir/r.t.	-	3%[f]	5%[f]	1%[f]	4%[f]	
H_2O_2	MeCN/$FeCl_3$/stir/r.t.	-	-	N.I.	-	-	h)

N.I. = Not Isolated; S.M. Starting Material (recovered)

a) Yields based on unrecovered [3.3.3]cyclazine diester (47a)

b) Tetrabutylammonium periodate (ref. 67)

c) Pyrdinium dichromate (ref. 68)

d) TEBA Benzyltriethylammonium chloride (a phase transfer catalyst)

cont.

Table 17 cont.

e) Obtained as an impure red solid; m/z 341; ^{1}H n.m.r. ($CDCl_3$) shows two AB systems and a singlet [δ9.01 (d)/7.50 (d); ^{3}J = 10.4 Hz; δ8.85 (d)/7.20 (d); ^{3}J = 9.9 Hz; 8.12 (s)]

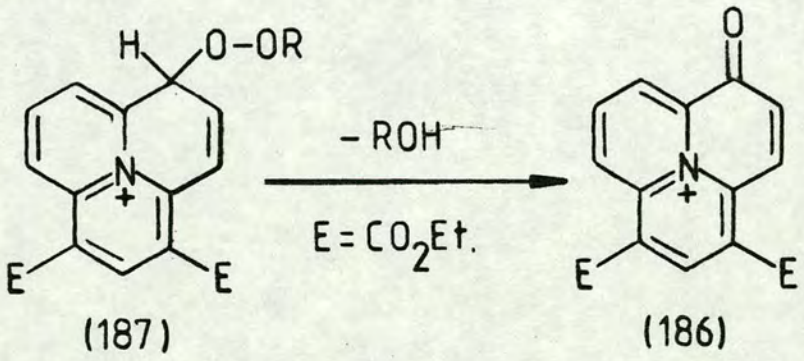
f) Crude yield

g) Also isolated was an orange-red oil; ^{1}H n.m.r. ($CDCl_3$) shows two AX spin systems [δ8.89 (d)/7.67 (d), ^{3}J = 8.9 Hz, δ8.25 (d)/6.88 (d), ^{3}J = 10.0 Hz]

h) Trace amount of a compound isolated that has a low Rf but does not match R1 or R2. Not isolated or characterised

Additional oxidation steps would then be necessary to generate the observed products. Thus the introduction of a carbonyl group at C-4 or C-6 of the cyclazine diester, leading ultimately to the [2.3.3]cyclazin-3- and 5-ones, might proceed according to Scheme 30 (where the radical cation and dication are shown in one canonical form only).

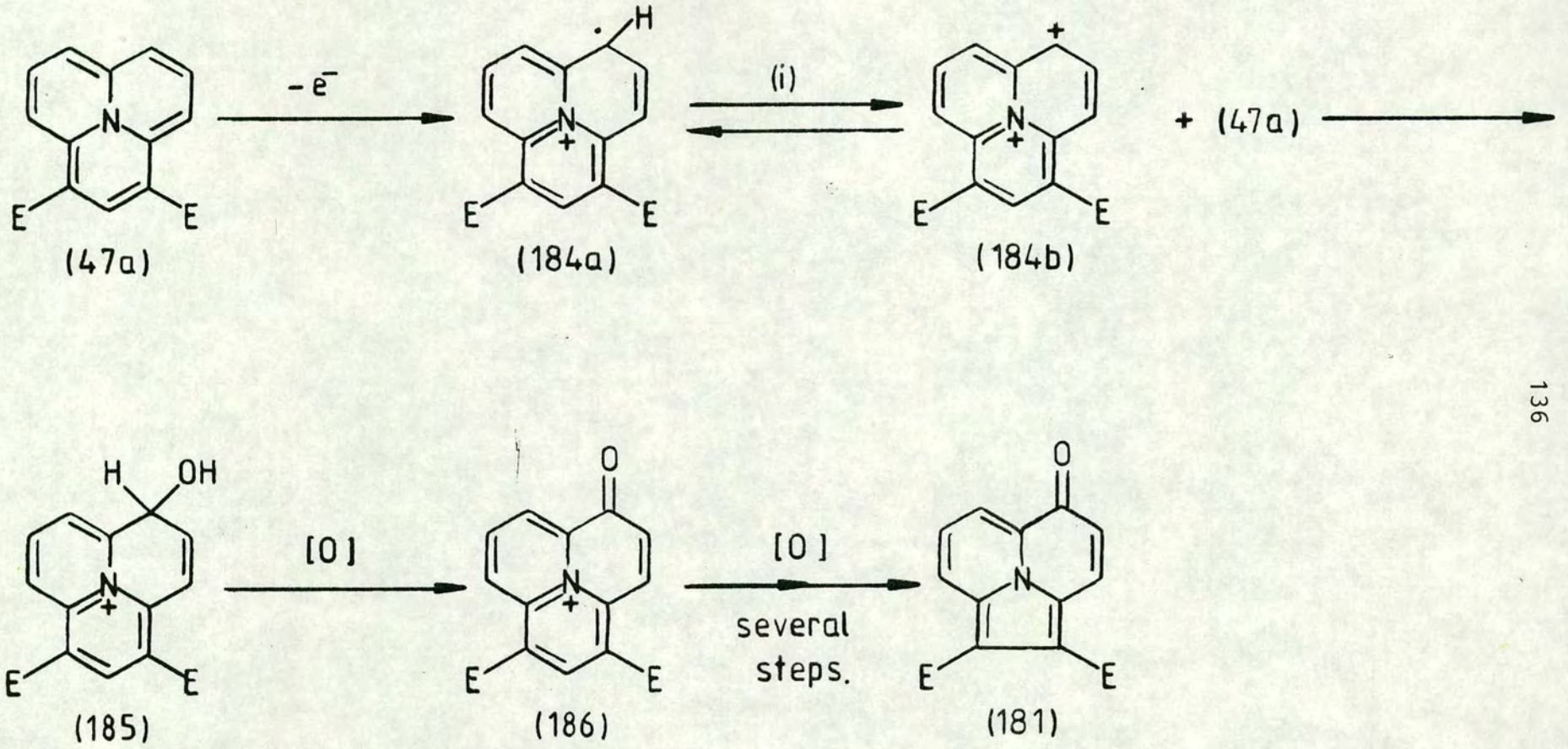
Based on this hypothesis, it seemed that one possible way to facilitate formation of the intermediate (186) would be to select an oxidant that generates peroxy-radicals (ROO·). These would be able to react with the cyclazine radical cation directly (i.e. without the intermediacy of the dication) and the resulting intermediate (187) would be convertible into the oxo-compound (186) by loss of ROH (Scheme 31).



(187) (186)

Scheme 31.

Although neither of the experiments with hydrogen peroxide had given encouraging results even in the presence of an electron transfer catalyst ($MnCl_2$), it was decided to try t-butyl hydroperoxide (Bu^tOOH) in the presence of a catalytic quantity of iron(III) chloride,



(i) Disproportionation.

Scheme 30.

an oxidant system which is known to generate both t-butylperoxy and t-butoxy radicals by the catalytic cycle[69]:-

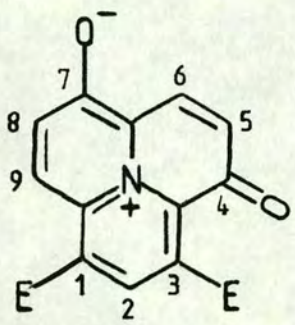
$$ROOH + Fe^{3+} \rightarrow ROO^{\cdot} + H^{+} + Fe^{2+}$$

$$ROOH + Fe^{2+} \rightarrow RO^{\cdot} + OH^{-} + Fe^{3+}$$

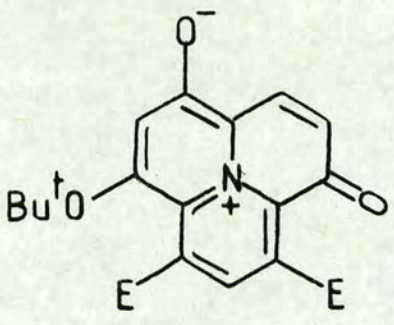
No appreciable reaction occurred at moderate temperatures when the cyclazine diester (47a) was treated with t-BuOOH alone but, when a catalytic amount of $FeCl_3$ was added, a rapid reaction took place and the initial yellow-green solution became a deep red colour. Analytical t.l.c. revealed that at least eight components were present and, of these, six were isolated. These included the [2.3.3]cyclazin-3-one (183) and -5-one (181) derivatives (10% and 12% respectively) as found in previous oxidations. Also isolated were four red compounds which will be designated R2A, R1, R1A and R2 in order of decreasing Rf value (silica) [the overall order being Y1, R2A, Y2, R1, R1A, R2]. The red products R1 and R2 were the same as those observed in previous oxidation reactions (see Table 17) and here they were both isolated in 3% yield.

The mass spectrum of both R1 and R2 showed molecular ion peaks M^{+} at m|z 341, corresponding to the [3.3.3]-cyclazine diester (47a) plus two oxygens and minus two hydrogens. The proton n.m.r. spectrum of R1 (Table 18) showed two AX systems at δ7.20(d) and 8.85(d) p.p.m. (^{3}J = 9.8 Hz), and δ7.51(d) and 9.00(d) (^{3}J = 10.4 Hz), and a singlet at δ8.11. This suggested an unsymmetrical structure (188), bearing O-substituents at C-4 and C-7,

Table 18. ^{1}H n.m.r. data (200 MHz) for R1, R1A, R2 and R2A in $CDCl_3$ (E = CO_2Et)

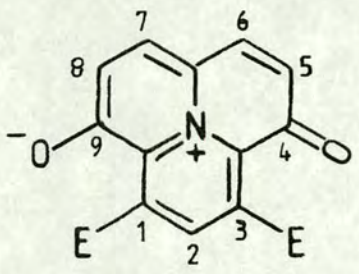


R1
(188)

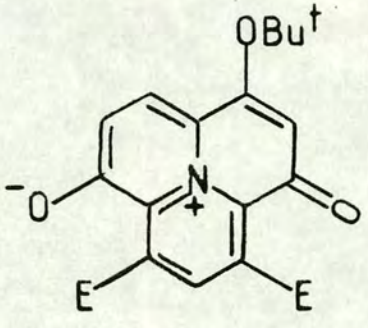


R1A
(191)

E = CO_2Et.



R2
(189)

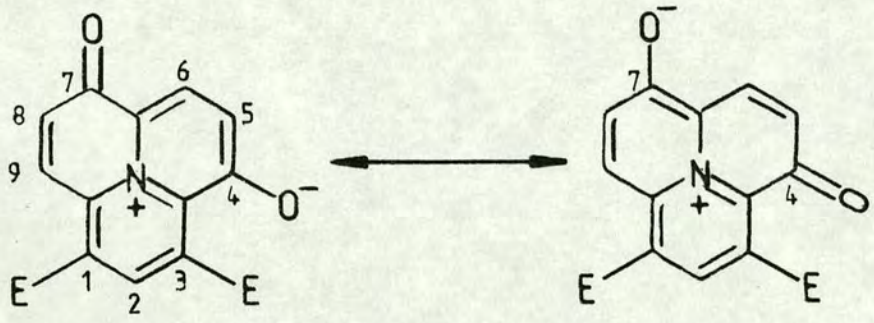


R2A
(190)

Compound	Position[b] δ/p.p.m.[a] 1(7)	2(8)	3(9)	4(1)	5(2)	6(3)	7(4)	8(5)	9(6)	Coupling constants J/Hz
(188)	[1.43 4.56]	8.11	[1.49 4.56]	-	7.20	8.85	-	7.51	9.00	$J_{5,6}$ 9.8; $J_{8,9}$ 10.4 Hz
(191)	[1,40 4.53]	7.50	[1.42 4.53]	-	7.14	8.76	-	7.01	(1.62)	$J_{5,6}$ 9.7 Hz
(189)	[1.43 4.55]	7.77	[1.43 4.55]	-	7.11	7.91	7.91	7.11	-	$J_{5,6}$ 9.7 Hz
(190)	[1.43 4.54]	7.65	[1.42 4.54]	-	6.79	(1.66)	8.42	7.10	-	$J_{7,8}$ 9.9 Hz

a) Values in parenthesis refer to protons in substituent groups
b) The unparenthesised numerals are those used in the discussion (ie. corresponding to starting material). Those given in parenthesis are the correct numbers according to the IUPAC rule that indicated hydrogen is given the lowest possible locant

which must be represented as a zwitterion, (an oxo[3.3.3]-cyclaziniumolate)*. The AX system with the higher coupling constant is assigned to the protons at C-8 and C-9 on the basis that the 8,9- bond, being represented as a double bond in both principal canonical structures (188a) and (188b), may be expected to have a higher bond order than the 5,6- bond which is double in (188b) and single in (188a).



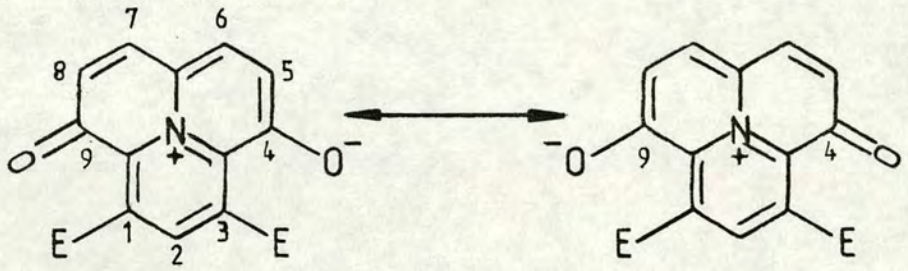
(188a) (188b)

E = CO_2Et.

---

* Compounds of this type are formally derivatives of the 1H-[3.3.3]cyclazinium ion and according to I.U.P.A.C. rules, the numbering system should start at the position of 'indicated hydrogen' which is here occupied by an oxo-substituent (see experimental section for full names). However, in order to facilitate this discussion, the original numbering system of the starting material (47a) is retained here (i.e. the ethoxycarbonyl groups are regarded as being at C-1 and C-3).

The other red solid (R2) had a more simple proton n.m.r. spectrum that showed only one AX pattern corresponding to four protons at δ7.11(d) and δ7.91(d) p.p.m. (^3J = 9.7 Hz), and a one-proton singlet at δ7.77. This indicated a symmetrical substitution pattern and the chemical shifts were consistent with substitution at C-4 and C-9 rather than C-6 and C-7, since there was no high frequency resonance comparable to that of H-9 in R1 (188). Thus the structure (189) was assigned to R2



(189a) (189b)

E = CO_2Et.

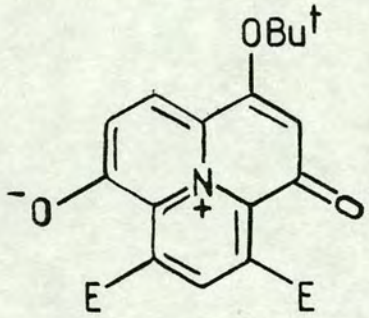
and this is consistent also with the AX coupling constant of 9.7 Hz which corresponds to the lower coupling constant ($J_{5,6}$) in R1.

The infrared spectrum of R1 showed peaks in the carbonyl stretching region at $\bar{\nu}_{max}$ 1720, 1630 and 1605 cm^{-1} and that of R2 at 1720 and 1620 cm^{-1}, corresponding to the ester groups and ring carbonyl absorptions.

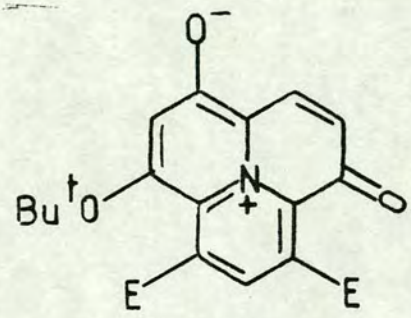
The other two red solids, R1A and R2A which were both collected in 5% yield were more difficult to identify,

since they showed evidence of t-butoxy substituents by n.m.r. and mass spectroscopy. The FAB mass spectrum of R1A showed a pseudo-molecular ion at m|z 414 $(M+H)^+$ and a strong fragment ion at 358 $(M+H - C_4H_8)^+$. The EI spectrum of R1A could not be obtained but that of R2A showed a true molecular ion ($M^{+\cdot}$) at m|z 413.

The ^1H n.m.r. spectra of R1A and R2A both showed a nine-proton singlet near δ1.6 and this, together with their mass spectra, suggested that the compounds were mono-t-butoxy derivatives of oxo[3.3.3]cyclaziniumolates. In principle, and assuming substitution of the cyclazine ring system only at ∝-positions, four such compounds are possible as shown in formulae (190) - (193). The aromatic region of the ^1H n.m.r. spectrum would be expected to show, for each of these structures, an AX system and two singlets. These features were indeed present in the spectrum of R1A and R2A but the value of J_{AX} was less



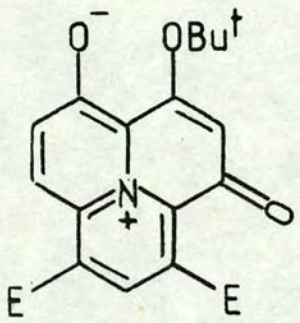
(190)



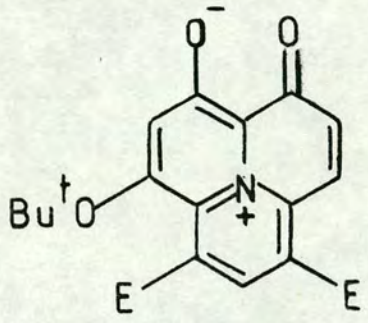
(191)

E = CO_2Et.

than 10 Hz for both compounds. This was thought to be inconsistent with coupling across a bond of high order (analagous to the 8,9-bond of R1) and structures (192) and (193) were therefore considered unlikely. It is also significant that the compound corresponding to (193)



(192)

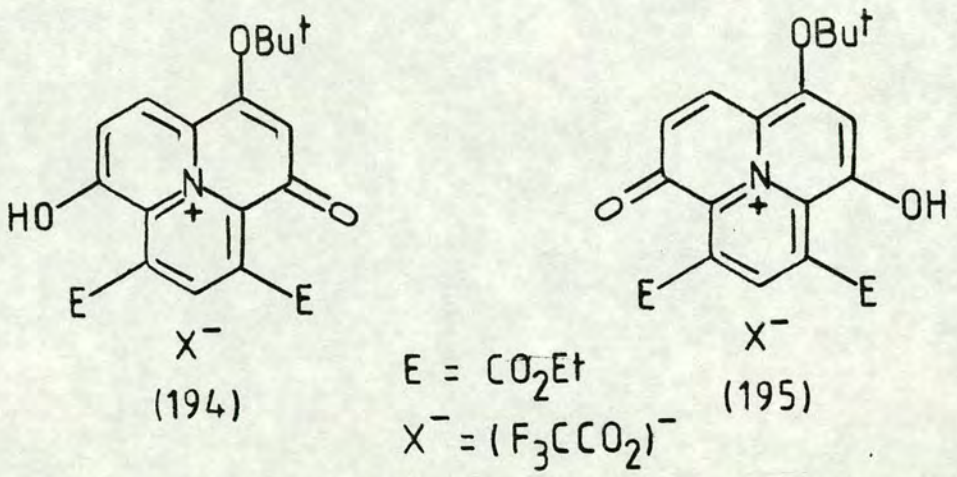


(193)

$E = CO_2Et$.

but lacking the t-butoxy-group was not detected among the products of oxidation. The chemical shifts for the AX system of R1A were very close (within 0.1 p.p.m.) to those of H-5 and H-6 in R1. It seemed probable therefore that R1A was a derivative (191) of R1 and that, by elimination, R2A was a derivative (190) of R2. The high frequency doublet of R2A was shifted to higher frequency by 0.5 p.p.m. relative to the corresponding doublet in R2 and this is consistent with the deshielding effect of a peri-t-butoxy substituent. Of the two singlets in the spectra of both R1A and R2A, that of lower frequency was assigned to the proton ortho to the (electron releasing) t-butoxy-group [Table 18]. Some proton n.m.r. experiments were conducted on the susceptibility of these oxo[3.3.3]cyclaziniumolates to protonation. When an n.m.r. sample of R2A dissolved in deuteriochloroform was treated with a few drops of trifluoroacetic acid (TFA), the solution colour changed immediately from a clear red to a clear orange, and the

resulting ^{1}H n.m.r. spectrum showed a mixture of two components present in approximately equivalent amounts (from the integral value of the t-butoxy singlets). In general, there had been a deshielding effect, all the aromatic resonances being shifted to a higher frequency, and the AX doublets, making allowance for some overlap, had been doubled in number. The ester resonances had also increased in complexity (full details of the n.m.r. spectrum may be found in the experimental section). The proton n.m.r. picture thus suggests a mixture of the two protonated forms (194) and (195). No further TFA experiments

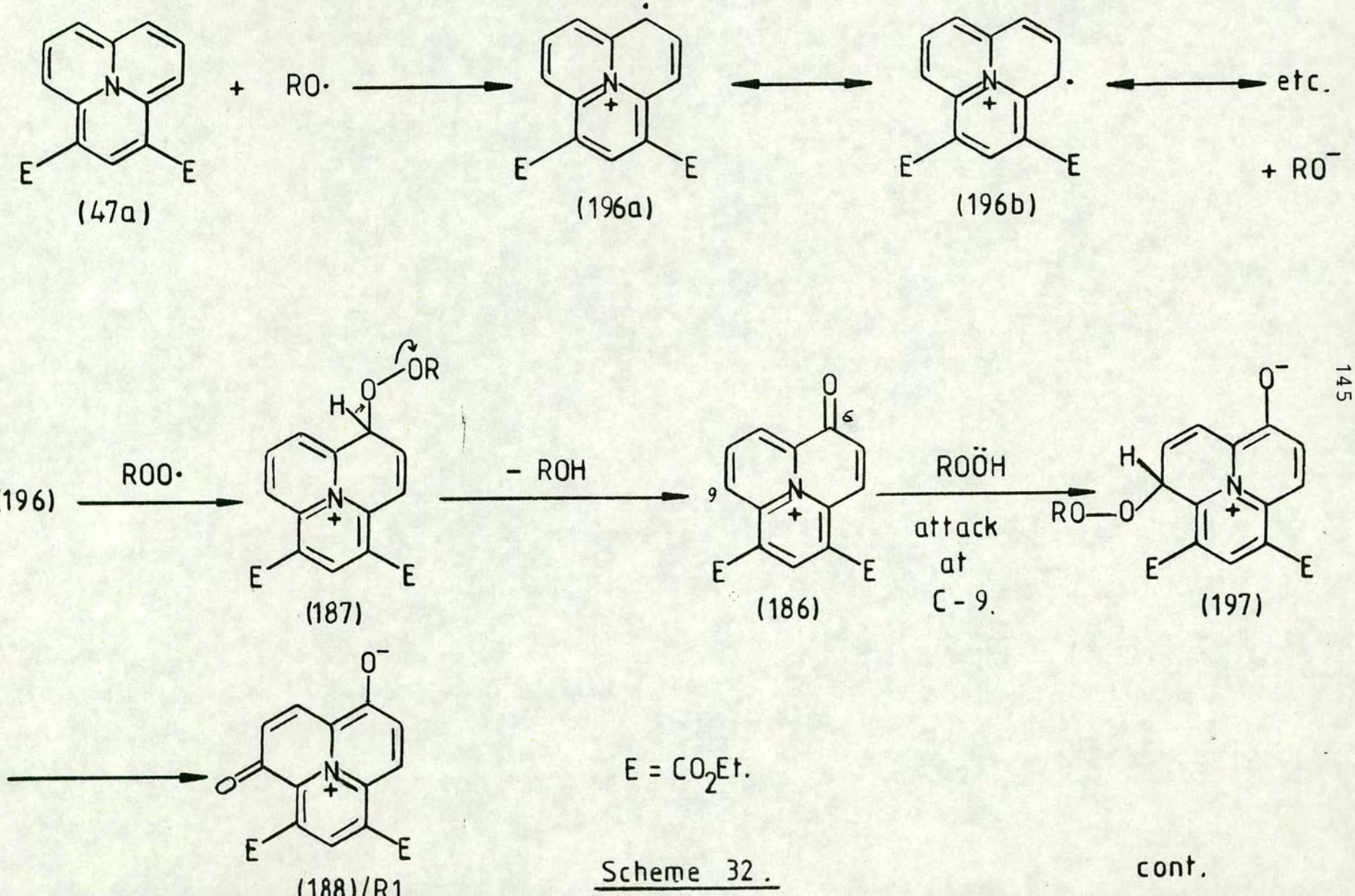


were carried out since it became obvious that protonation of the oxo[3.3.3]cyclaziniumolates would only lead to more complex n.m.r. spectra owing to the possibility of more than one protonation site for each compound.

Although product yields were not high from these oxidation experiments, the combination of t-butyl hydroperoxide and iron(III) chloride was a distinct improvement on other reagents for the oxidation of the cyclazine diester. Not only were the [2.3.3]cyclazinones

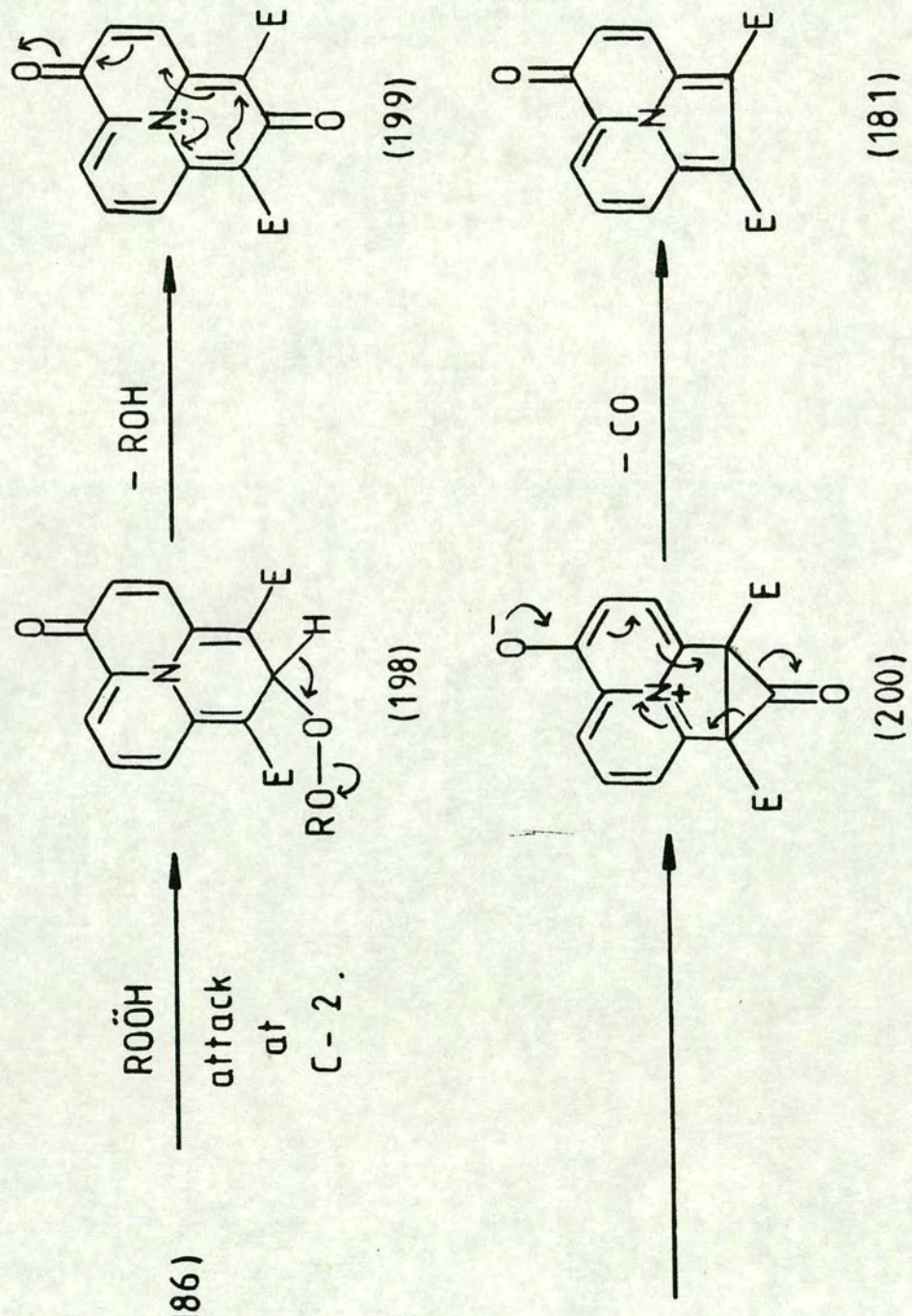
formed but also the two red products (R1) and (R2) were obtained, for the first time, in sufficient amounts for a positive identification. Since the reasoning that led to the choice of this reagent system was based on mechanistic speculation, the success of the reaction lends some support to the hypothesis embodied in Schemes (30) and (31). It is now appropriate, therefore, to speculate in more detail concerning the possible mode of formation of the various products.

As outlined previously, the first stage of the reaction is considered to be an electron-transfer step leading to the cyclazine radical cation (196). Since t-butyl hydroperoxide alone was not effective in causing oxidation, it seems likely that the electron-acceptor in this redox process is a radical species, such as the t-butoxy radical, produced by catalytic decomposition of the hydroperoxide. The radical cation (196) is then considered to combine with a t-butylperoxy radical at either of the two free α-positions as illustrated in Scheme (32) for combination at C-6. Elimination of t-butyl alcohol from the resulting adduct (187) would then generate an oxocyclazinium ion intermediate (186). Subsequent nucleophilic attack by a peroxide molecule could take place at C-9 and further elimination of t-butyl alcohol would lead to the oxocyclaziniumolate (188) (ie. R1). A similar sequence of reactions involving initial combination of the radical cation with a t-butylperoxy radical at C-4, could lead either to R1 or to R2. The t-butoxy-substituted



Scheme 32.

cont.



Scheme 32. [cont.]

compounds R1A and R2A are possibly secondary products arising from free radical substitution reactions of R1 and R2.

It is possible that the [2.3.3]cyclazinones found in this work are also formed from the proposed intermediate (186) by addition of the peroxide at C-2 followed by elimination of t-butyl alcohol. Instead of yielding an oxocyclaziniumolate, this process would lead to a [3.3.3]cyclazine-2,4- or 2,6-quinone (e.g. 199). Internal rearrangement could then be envisaged as giving an intermediate (200) containing a cyclopropanone moiety which could extrude carbon monoxide to give the observed 3- and 5-[2.3.3]cyclazinones.

The reaction pathways outlined above are of course highly speculative and exceedingly difficult to verify. As a whole, however, they form a useful working hypothesis upon which the design of further experiments might be based.

4.3.2 Isolation of two oxidative degradation products of the parent [3.3.3]cyclazine

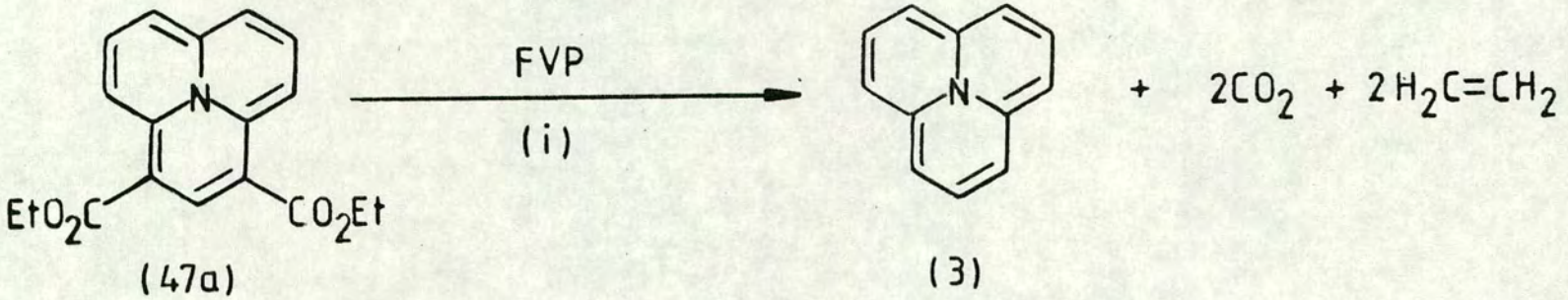
As mentioned in the previous section, Leupin and his co-workers[27b] noted the presence of fluorescent species formed by oxidative degradation of the parent [3.3.3]-cyclazine (3) during their spectroscopic work, but they were unable to isolate and characterise these materials.

In the present work, during an attempt to generate and isolate the parent [3.3.3]cyclazine (3) by flash

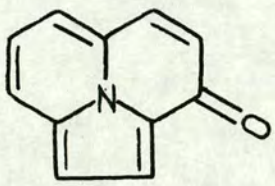
vacuum pyrolysis (fvp), these oxidation products were isolated. The parent cyclazine (3), obvious from its characteristic metallic purple colour[22], was generated by flash vacuum pyrolysis at 850°C of the 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine (47a) [Scheme (33)]. An apparatus designed to exclude oxygen (air) at all stages of the operation was used, since the parent [3.3.3]cyclazine (3) is known[22] to be unstable in the presence of air. However, during dissolution of the product in d^6-benzene for n.m.r. purposes, the purple solid darkened to brown, and no proton resonances were observed in the expected regions of the n.m.r. spectrum. Thus, it appeared that partial or complete oxidation had occurred due to inadvertent admission of air, despite all the precautions to avoid such an occurrence.

The n.m.r. samples of the pyrolysate (in d^6-benzene) changed via a dark brown to a purple-blue colour. This purple colour was discharged by shaking the benzene solution with aqueous sodium dithionite, which gave rise to a pale yellow-green organic solution, fluorescent under u.v. light. Subsequent extraction of the organic materials into dichloromethane and evaporation of the extract gave a residue which, when tested by t.l.c. (silica), showed spots coincident with authentic samples of the parent 3- and 5-[2.3.3]cyclazinones (34) and (37), the 5- isomer being the more fluorescent.

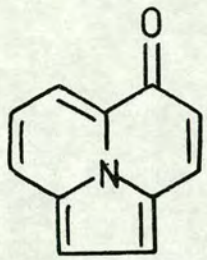
The components were separated by preparative t.l.c.


FVP
(i)
+ 2CO2 + 2H2C=CH2
EtO2C
CO2Et
(47a)
(3)
[O]
Conditions:-
(i) 850°C / 0·001 torr.
(34)
+
(37)

Scheme 33.



(34)



(37)

on silica, to give small amounts of (34) and (37), which were subsequently identified by their mass spectra and by comparison of their ^{1}H n.m.r. spectra with those of authentic samples obtained previously[6] in these laboratories.

Thus the oxidative degradation of the parent [3.3.3]-cyclazine shows analogy to that of its 1,3-diester, the corresponding [2.3.3]cyclazin-3- and -5-ones being isolable products from both compounds. It is probable that these compounds (34) and (37) account for the additional fluorescent emission observed by Leupin et al[27b] in their spectroscopic work on the parent [3.3.3]cyclazine (3).

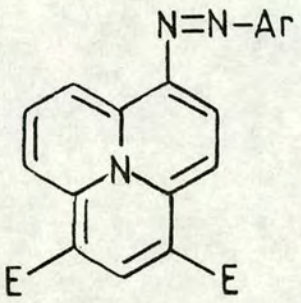
4.4 Miscellaneous Reactions

This short section contains some reactions that do not fit into any of the previous categories.

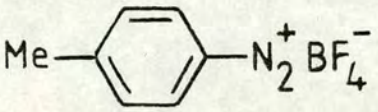
4.4.1 Reaction of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with a diazonium salt

The work described in this section was carried out to test the idea that the [3.3.3]cyclazine diester (47a),

being electron-rich and susceptible to electrophilic substitution, might couple with a diazonium salt to give an arylazo-derivative such as compound (201) or the C-4 substituted equivalent.



(201)



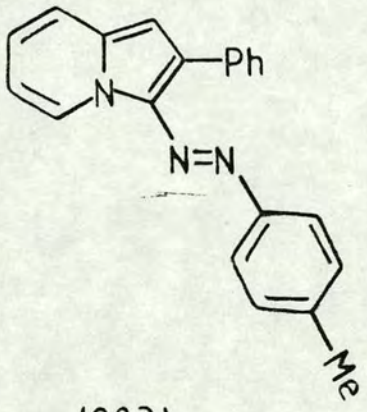
(202)

Since it was desirable to avoid an aqueous medium, a solid diazonium salt[70] (202) was chosen for this reaction. When the reagent (202) and the cyclazine diester (47a) were stirred together at 0°C in acetonitrile in the presence of an acid scavenger (eg. K_2CO_3), effervescence was observed and t.l.c. showed mainly dark material of low chromatographic mobility and traces of several products at higher Rf. Thus, although some cyclazine remained after 4.5 hours most of the starting material appeared to have decomposed and no work-up was performed as the minor components of the mixture were not well separated on t.l.c..

The reaction was then repeated using 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) as the acid scavenger, but a similar complex reaction mixture resulted.

Preparative t.l.c. failed to separate the components and no characterisable products were obtained. Further small scale tests revealed that the base, DBU, reacted to a small extent with the diazonium salt (202), and this could have increased the complexity of the reaction mixture.

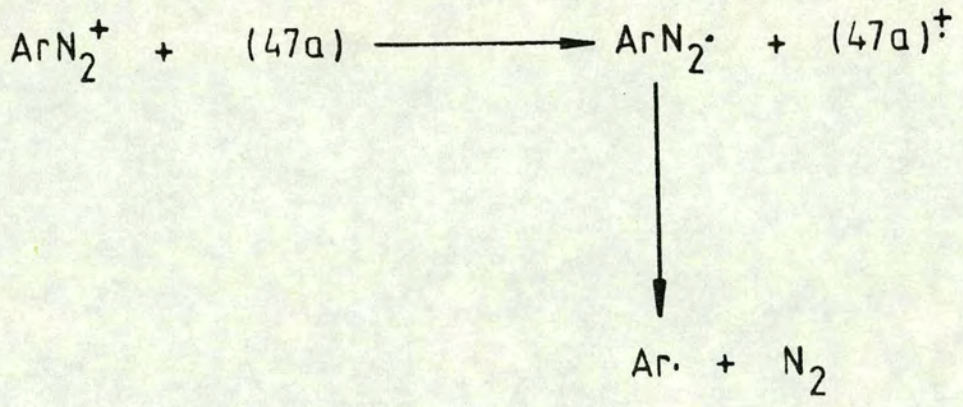
When the same diazonium salt (202) was tested with 2-phenylindolizine under similar conditions, an immediate red colour was produced and no gas was evolved. This was taken to indicate formation of the arylazo-compound (203), thus showing that a typical electron-rich heterocycle does undergo azo-coupling under the conditions employed. The failure of the diazonium salt to couple



(203)

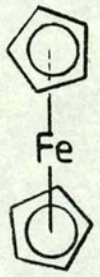
with the [3.3.3]cyclazine diester (47a) may be due to the susceptibility of the cyclazine derivative to oxidation by an electron-transfer process as outlined in Scheme 34. The gas that was evolved during these reactions and during other small scale tests using alternative bases, was most likely nitrogen from the decomposition of the

diazonium salt (202). This gas was also evolved when the cyclazine was treated with the diazonium salt at 0°C in acetonitrile in the absence of any base.



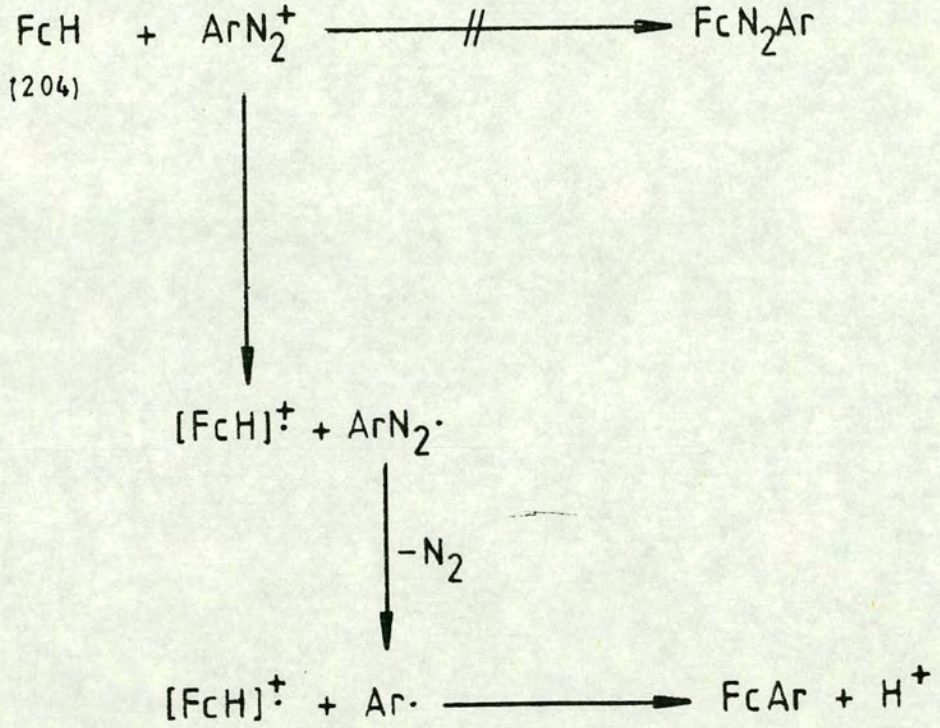
Scheme 34.

Attempts to couple ferrocene (204) with diazonium salts have met with similar failure, leading only to arylferrocenes rather than arylazoferrocenes, and a similar explanation[71] has been offered in terms of the facile oxidation of ferrocene to the ferricenium ion (Scheme 35). Although no aryl derivatives were isolated from the corresponding reaction with the cyclazine (47a), it is possible that one or more of the minor spots



≡ FcH

(204)



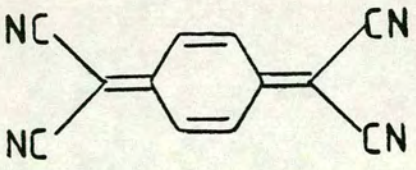
Scheme 35.

Scheme 35

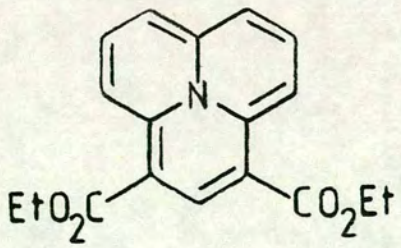
observed on t.l.c. plates could have been due to products of arylation.

4.4.2 Reaction of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with tetracyanoquinodimethane

Many types of π-electron-rich carbo- and hetero-cyclic system react with tetracyanoquinodimethane (TCNQ) (205) to give π-donor-acceptor complexes[72] some of which



(205)

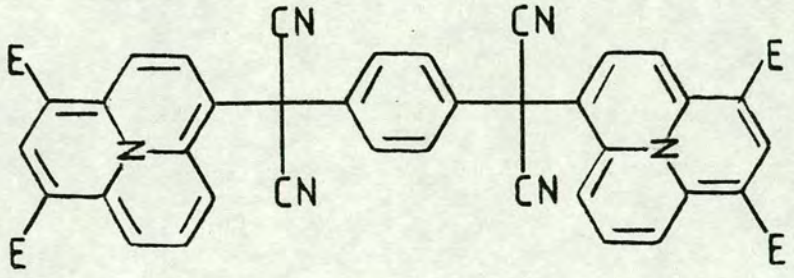


(47a)

have attracted much recent interest because of their high electrical conductivities. Since the [3.3.3]cyclazine diester (47a) is an electron-rich species, it was decided to try to form such a complex between this cyclazine and TCNQ.

When the [3.3.3]cyclazine diester (47a) was treated with an equimolar amount of TCNQ in acetonitrile, either at room temperature or at reflux temperature, a brown solid precipitated. This product could not be recrystallised but some purification was achieved by Soxhlet extraction with ether to remove small amounts of more soluble impurities. The ^{1}H n.m.r. spectrum (Table 19) of the residual brown solid showed an AMX system at δ4.69, 6.14 and 6.87 (^{3}J = 9.1 Hz, ^{4}J = 1.4 Hz) and an AB system at δ6.28 and 6.54 (^{3}J = 9.1 Hz) which together indicated that 6-substitution had occurred in (47a). The spectrum also contained two singlets, one at δ7.77 and one at δ7.22 which were most likely due to four aromatic protons derived from the TCNQ and to H-2 of the [3.3.3]cyclazine nucleus respectively. Since these singlets were in the intensity ratio 2:1, it was apparent that the product had been formed from two molecules of (47a) and one of TCNQ. The mass spectrum of this product could not be obtained under EI conditions, but using a FAB technique with a matrix of 3-nitrobenzyl alcohol[96], the expected parent ion (m|z 824 [$M^{\cdot+}$]) was observed. The u.v.-visible spectrum was closely similar to that of (47a), confirming the

presence of a relatively unperturbed cyclazine substructure. The infrared spectrum showed a carbonyl band at 1675 cm^{-1}, but no C≡N stretching band. The absence of a cyano band does not necessarily mean that no cyano groups are present, since literature[73] reports state that the intensity of this absorption varies greatly and that in some cases no absorption is visible. A CHN analysis of the material was unsatisfactory but the result was in better agreement with a (47a):TCNQ ratio of 2:1 than with any other ratio. From the above data the brown solid was clearly not a charge transfer complex but probably a substitution product (206) containing two cyclazine moieties linked, via their C-6 positions, through a bridging unit derived from TCNQ. This structure was in very good agreement with the ^1H n.m.r. data (as shown in Table 19) and with the information obtained from the FAB mass spectrum.



(206)

E = CO_2Et.

SECTION 5

5. Investigation of flash vacuum pyrolysis as a route to cyclazines

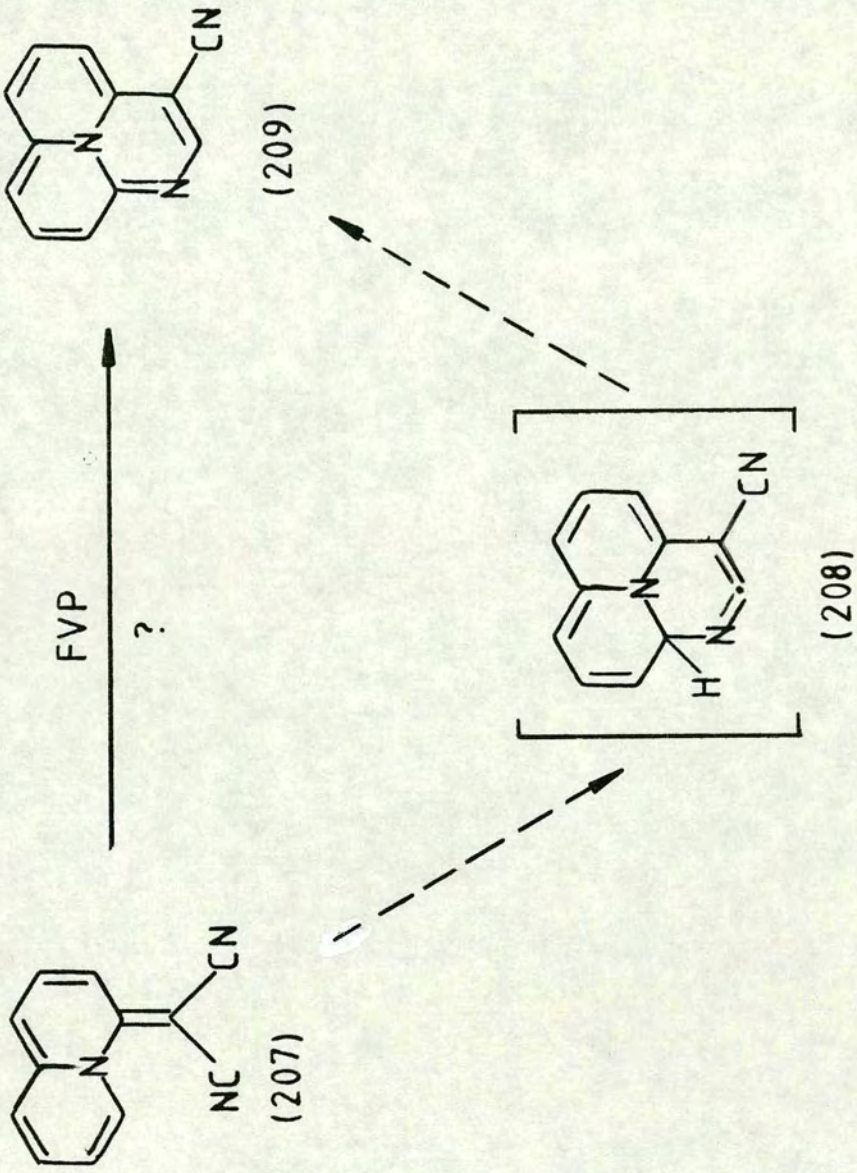
5.1 Introduction

The previously described (section 2) new synthetic route to [3.3.3]cyclazines (47) proceeds via a bicyclic (quinolizine) precursor and depends on an electrocyclic ring closure to form the third ring. An extension of this principle to the synthesis of aza[3.3.3]cyclazines seemed possible, and the experiments described in this section were based on the idea that final ring closure might occur under the conditions of flash vacuum pyrolysis (fvp). However, no azacyclazines were obtained from these experiments, but a novel rearrangement of the quinolizine ring system was discovered.

5.2 FVP as a route to aza[3.3.3]cyclazines

5.2.1 Attempts to generate 1-aza[3.3.3]cyclazines

Aza[3.3.3]cyclazines are known to be stabilised if the aza-substituent is in an α-position of the cyclazine periphery (see Introduction/Section 3.2). Thus the 1-aza-3-cyano-compound (209) would be doubly stabilised and it seemed possible that this compound might be formed by thermal isomerisation of the known quinolizinylidene-malononitrile (207) as outlined in Scheme 36. It was envisaged that the cyclisation would proceed via a highly strained (non-linear) keten-imine intermediate (208),



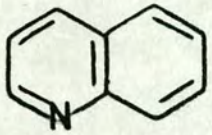
Scheme 36.

followed by a hydrogen shift to give the aza[3.3.3]-cyclazine (209).

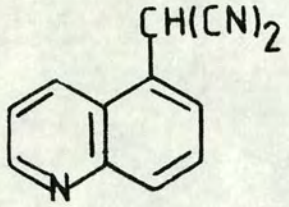
No change was observed when the quinolizinylidene-malononitrile (207) was heated for five hours in boiling 1,2,4-trichlorobenzene (214°C), but a reaction occurred under fvp conditions (800°C; 0.005 mmHg) and a blue solid collected in the pyrolysate cold trap. T.l.c. of this material revealed that it was a mixture and the three major components of the mixture were isolated by flash column chromatography on silica. Mass spectrometry showed each product to have a molecular weight of 193, the same as the starting material. The products will be designated FVP1, FVP2 and FVP3 in order of decreasing Rf value on silica t.l.c..

The major product, FVP3 (18% yield), was a blue solid which was identified as a quinoline derivative (210A) by its spectroscopic properties. The compound gave blue-green solutions in polar solvents such as ethanol and acetone and yellow solutions in non-polar solvents such as diethyl ether. This dependence of colour on solvent polarity, and the blue colour of the solid, were attributed to the presence of a minor tautomeric form (210B) which, owing to extensive conjugation from the N lone-pair to the cyano-groups, would be expected to be highly coloured. The electronic spectrum of this compound (Table 20, experimental section and Fig. 4) was similar to that of quinoline, but

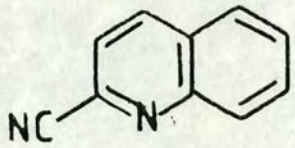
Table 20. U.V. spectroscopic data for the quinoline series of isolated compounds



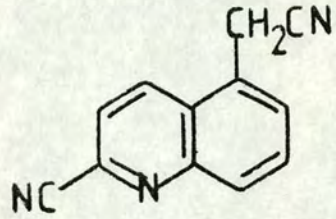
(230)



(210)
FVP3



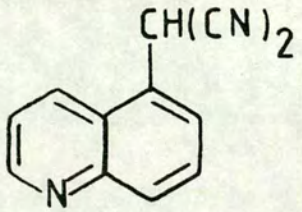
(231)



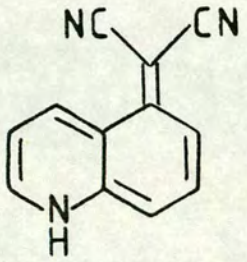
(213)
FVP2

Compound	U.V. Solvent	λ_{max}/nm ($\log_{10}\varepsilon$)				
(230)	EtOH		230 (4.4)	276 (3.6)	301 (3.5)	314 (3.6)
FVP3 (210)	EtOH[a]	218 (4.6)	233 (4.2)	281 (4.0)	301 (3.9)	315 (3.7)
FVP3	THF			273 (3.9)	301 (3.6)	314 (3.6)
FVP3	CH_2Cl_2 (EtOH free)		229 (4.3)	274 (3.9)	302 (3.6)	316 (3.8)
(231)	EtOH[b]			295 (3.6)	320 (3.4)	330 (3.3)
FVP2 (213)	EtOH	208 (4.6)	240 (4.9)	291 (3.7)	318 (3.6)	332 (3.4)

a Also visible is a broad band, λmax 593 nm (3.0) when a concentration of 9.83×10^{-4} mol.l^{-1} is used (10 x concentration used for other calculations).
b Literature data (N. Hata and T. Saito, Bull.Chem.Soc.Jap., 1974, 47, 942.)

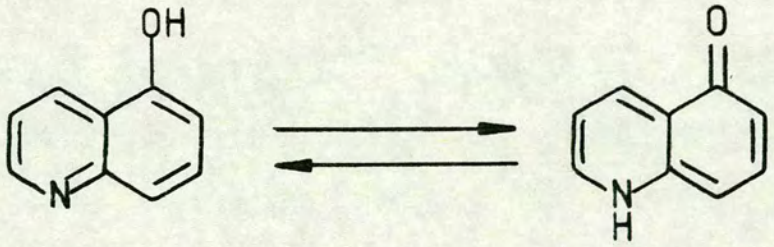


(210a)



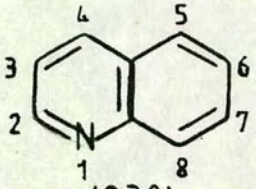
(210b)

contained an extra (weak) peak in the visible region (λ 593 nm) when the spectrum was run in ethanol, relative to the spectra run in THF and dichloromethane, which did not exhibit this high wavelength absorption. This extra absorption is attributed to the NH tautomer (210B). It has been suggested[74] that a similar type of tautomerism occurs in 5-hydroxyquinoline (211):-

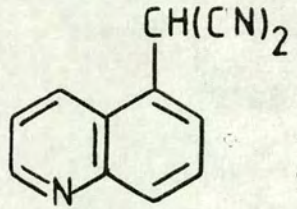


(211a) (211b)

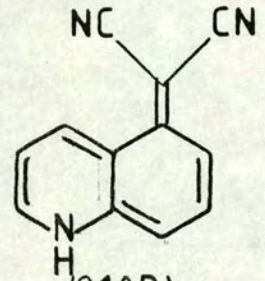
The proton n.m.r. spectrum of FVP3 (210) [in $CDCl_3$] showed the characteristic resonances expected for a substituted quinoline (Table 21/experimental section). In particular, the two outermost signals in the aromatic



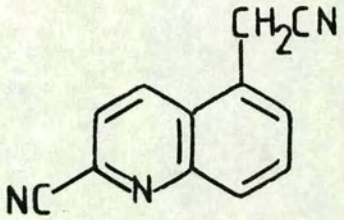
(230)



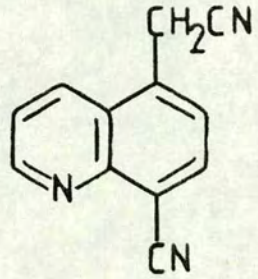
(210A)
FVP3



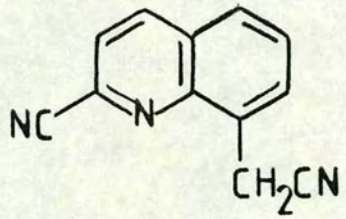
(210B)



(213)
FVP2



(214)
FVP1A



(216)
FVP1B

Table 21. Proton n.m.r. spectra of the Quinoline series

δ/H	Solvent	H-2	H-3	H-4	H-5	H-6	H-7	H-8	Coupling constants, J/Hz
(230)	CCl_4 [a]	8.82	7.31	8.05	7.73	7.46	7.65	8.05	$J_{2,3}$ 4.2; $J_{2,4}$ 1.8; $J_{3,4}$ 8.2; $J_{4,8}$ 0.8; $J_{5,6}$ 8.2; $J_{5,7}$ 1.5; $J_{5,8}$ 0.7; $J_{6,7}$ 6.9; $J_{6,8}$ 1.2; $J_{7,8}$ 8.6 Hz
(230)	$CDCl_3$ [b]	8.82 (dd)	7.23 (dd)	7.98 (ddd)	7.66 (m)	7.41 (ddd)	7.60 (ddd)	8.05 (m)	$J_{2,3}$ 4.2; $J_{2,4}$ 1.8; $J_{3,4}$ 8.3; $J_{4,8}$ 0.7; $J_{5,6}$ 8.1; $J_{5,7}$ 1.6 $J_{5,8}$ 0.8; $J_{6,7}$ 6.9; $J_{6,8}$ 1.2; $J_{7,8}$ 8.5 Hz
(230)	d^6-acetone [c]	8.90	7.47	8.29	7.92	7.54	7.74	8.07	$J_{2,3}$ 4.2; $J_{3,4}$ 8.3; $J_{5,6}$ 8.0; $J_{6,7}$ 6.8; $J_{7,8}$ 8.6 Hz
FVP3 (210)	$CDCl_3$ [b]	9.07 (dd)	7.62 (dd)	8.29 (m) [d]	(5.54) (s)	7.7-7.9 ⟷ (m)		8.33 (m) [d]	$J_{2,3}$ 4.3; $J_{2,4}$ 1.5; $J_{3,4}$ 8.6 Hz; other couplings obscured. (J indeterminate)
FVP3 (210)	d^6-acetone [b]	9.08 (dd)	7.77 (dd)	8.69 (br.d)	(6.7) (br.s)	7.8-8.0 ⟷ (m)		8.24 (br.d)	$J_{2,3}$ 4.1; $J_{2,4}$ 1.2; $J_{3,4}$ 8.7 Hz; $J_{6,7}/J_{6,8}/J_{7,8}$ indeterminate
FVP2 (213)	$CDCl_3$ [b]	-	7.82 (d)	8.41 (dd)	(4.16) (s)	7.7-7.9 ⟷ (m)		8.20 (ddd)	$J_{3,4}$ 8.7; $J_{6,7}$ indet.; $J_{6,8}$ 2.2; $J_{4,8}$ ~0.9 Hz other couplings indeterminate
FVP1A (214)	$CDCl_3$ [b]	9.06 (dd)	7.69 (dd)	8.58 (dd)	(4.49) (d)	7.96 (dt)	8.02 (d)	-	$J_{2,3}$ 4.2; $J_{2,4}$ 1.7; $J_{3,4}$ 8.5; $J_{6,7}$ 7.5; $J_{CH_2C_6}$ ~0.9 Hz
FVP1B (216)	$CDCl_3$ [b]	-	7.77 (d)	8.35 (d)	7.9 (br.d)	7.7 (dd)	8.1 (dd)	(4.44) (s)	$J_{3,4}$ 8.4; $J_{5,6}$ ~8; $J_{6,7}$ ~ 7 Hz; other couplings indeterminate

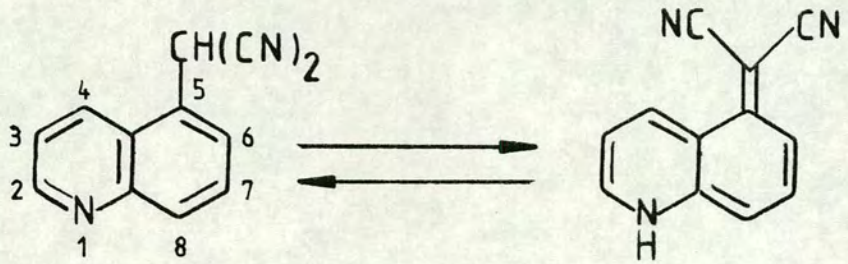
a Spectrum from literature (ref. F.Taddei et al, Org.Mag.Res., 1975, 7, 451)
b 200 MHz proton n.m.r. spectrum. Substituent groups are shown in parenthesis
c Spectrum from literature (ref. P.J. Black and M.L. Heffernan, Aust.J.Chem., 1964, 17, 558)
d possibly mt

region (δ9.07 (dd) and δ7.62(dd) were easily recognised as being due to H-2 and H-3, respectively, of a pyridine ring, the coupling constants ($J_{2,3}$ 4.2; $J_{3,4}$ 8.6; $J_{2,4}$ 1.5 Hz) being characteristic[75,76] of such a structural feature. The signals due to H-4 (δ8.29) and H-8 (δ8.33) showed partial overlap and those of H-6 and H-7 were recognisable as the XY part of an AXY spin system (A = H-8) at δ7.7-7.9. The only remaining feature of the spectrum was a sharp one-proton singlet at δ5.54 attributable to the deshielded saturated proton of the $CH(CN)_2$ group.

When the proton n.m.r. spectrum of FVP3 was run in d^6-acetone, the most noticeable change was a shift of the H-4 resonance to higher frequency, resulting in a separation of this signal from that due to H-8. A corresponding solvent shift occurs in the spectrum of quinoline (Table 21). However, there was also considerable peak broadening resulting in complete loss of fine coupling from the H-4 and H-8 peaks. Similarly, the singlet at δ5.54 was not present in the d^6-acetone spectrum, but instead a broad hump was present at δ6.7. It is possible that the line broadening was due to an exchange process involving the small amount of the tautomer (210B).

The ^{13}C n.m.r. spectrum (in $CDCl_3$) [Table 22] of the blue pyrolysis product (FVP3) showed the expected six sp^2-CH resonances and three sp^2-C quaternary resonances corresponding to the quinoline ring system. In addition

Table 22. ^{13}C n.m.r. data for compound FVP3



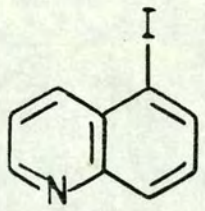
(210A) (210B)

a) 90.56MHz ^{13}C n.m.r.
b) 50.32MHz ^{13}C n.m.r.

δ(CDCl$_3$)[a]		Assignment	δ(d^6-acetone)[b]		Assignment
25.8		CH(CN)$_2$	24.9		CH(CN)$_2$
111.1	q	2 x C≡N	112.1		2 x C≡N
121.9	q	C-5	121.5		C-3
122.5		C-3	124.0	q	C-4a
124.6	q	C-4a	126.3		C-6
127.6		C-6	128.5		C-8
128.9		C-8	130.0		C-7
129.7		C-7	131.1		C-4
133.3		C-4	131.2		C-5
148.7	q	C-8a	147.9	q	C-8a
151.3		C-2	150.4		C-2

to these signals, the cyano group quaternaries gave a single peak at δ 111.1 and the sp^3-$\underline{C}(CN)_2$ resonance was present at δ 25.8, thus accounting for all the carbons.

As a final proof that the product FVP3 was indeed 5-(dicyanomethyl)quinoline (210), it was decided to undertake an unambiguous synthesis of this compound from 5-iodoquinoline (212). Attempts to replace the iodine by reaction with the anion of malononitrile in

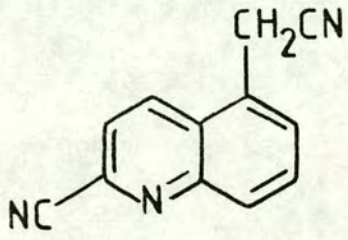


(212)

the presence of bis(triphenylphosphine)palladium(II) dichloride[77] failed, but a similar reaction in the presence of copper(I) iodide[78] gave trace amounts of the desired blue compound, clearly visible by analytical t.l.c.. Isolation of the blue material by preparative t.l.c. gave an insufficient amount of the material for complete purification. A complete set of spectroscopic data for the synthetic product could not be obtained, but those peaks in both the u.v. and ^1H n.m.r. spectra that were not obscured by absorptions due to impurities coincided with peaks in the corresponding regions of the spectra of FVP3. The thin layer chromatographic behaviour of the two samples was identical. Lack of time prevented further

work to improve the synthetic procedure.

The pyrolysis product obtained in the second highest yield (8%) was FVP2, a pale bluish-grey solid, the spectroscopic properties of which provided evidence for the structure (213). The ^{1}H n.m.r. spectrum (Table 21)

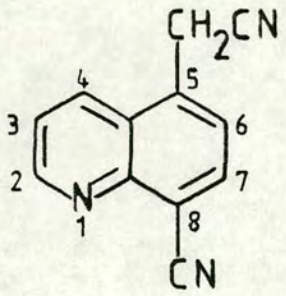


(213)
FVP2

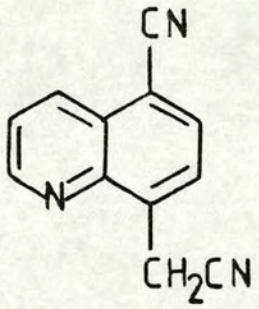
of this compound contained no high frequency signal corresponding to an α-pyridine proton but the remaining signals in the aromatic region were consistent with the presence of a quinoline ring system. The resonance due to H-4 was well-resolved at δ8.41 ($J_{3,4}$ 8.7 Hz) and showed additional long range coupling to H-8 ($J_{4,8}$ ~ 0.9 Hz), a well-documented[76] feature of quinoline n.m.r. spectra. The H-3 doublet, distinguished by its line separation ($J_{3,4}$), was present as part of a three-proton multiplet at δ7.7-7.9, and the H-8 signal at δ8.20 was close to its expected position. In the aliphatic region, a two-proton singlet at δ4.49 was good evidence for the presence of the CH_2CN group. DEPT and Quatgen ^{13}C n.m.r. spectroscopy [Table 23] confirmed that the compound contained a CH_2 group (δ21.1), five sp^2-CH carbons, and six quaternary

carbons, including two peaks at δ116.4 and 117.0 for the two different cyano groups. The ultraviolet spectrum of FVP2 differed from that of quinoline and FVP3, but was similar to that of 2-cyanoquinoline (see Table 20, Fig. 6 , experimental section).

The pyrolysis product FVP1 was isolated as yellow prisms in 2% yield. Its proton n.m.r. spectrum (Table 21) showed that it contained a major component (FVP1A), which was a 5,8-disubstituted quinoline, and a minor component (FVP1B) which was probably yet another isomeric quinoline derivative. The structure (214) was assigned



(214)
FVP1A

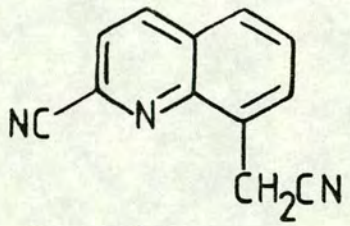


(215)

to FVP1A on the basis of the stronger set of peaks in the ^{1}H n.m.r. spectrum, comprising (a) an AMX spin system, due to H-2, 4 and 3, which was closely similar to the corresponding spin system in FVP3, and (b) an AB system, centred at δ8.0 and due to H-6 and 7 ($J_{6,7}$ 7.5 Hz). The low frequency component of the AB system showed an additional triplet splitting ($^4J \sim 0.9$ Hz) arising from coupling to the CH_2 group. The alternative structure (215)

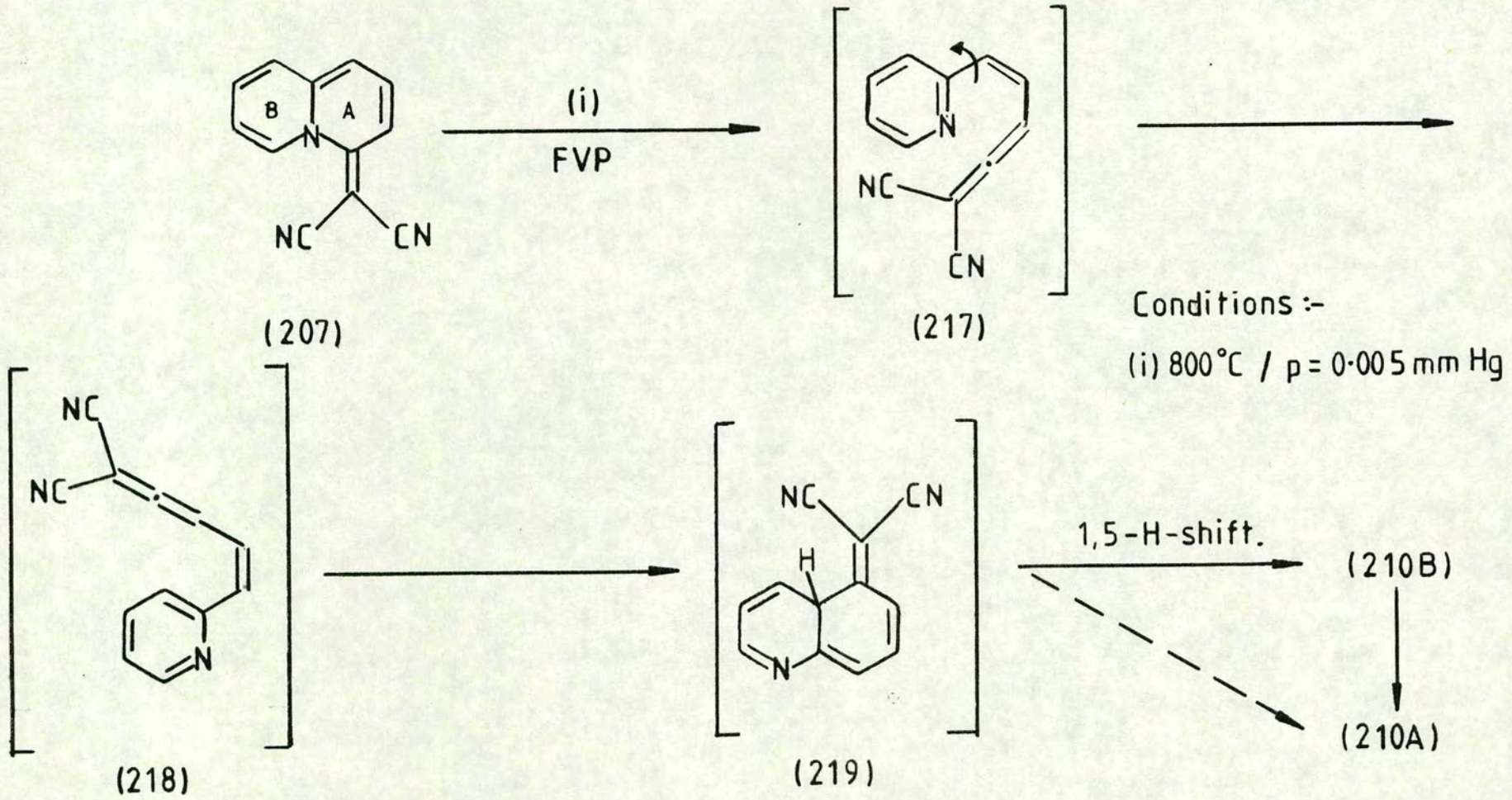
cannot be excluded but (214) is considered to be more likely because of its closer relationship to FVP3.

The ^1H n.m.r. peaks due to the minor component (FVP1B) though interspersed with those of FVP1A, were quite clearly visible and comprised two quite independent spin systems. One of these was an AX system which, from its chemical shifts (δ7.77 and 8.35) and coupling constant (J_{AX} 8.4 Hz) was assigned to H-3 and H-4 in a 2-cyanoquinoline. Since H-4 showed no additional coupling, the absence of H-8 could be inferred. The other spin system, of AMX type, was assigned to H-7 (δ8.1), H-5 (δ7.9), and H-6 (δ7.7), thus pointing to (216) as the most likely structure for FVP1B.



(216)
FVP1B

The isolation of these products from the fvp reaction now requires some mechanistic discussion. The formation of the major product (FVP3) in this high temperature vapour phase process can be explained in terms of a mechanism (Scheme 37) that involves electrocyclic opening of ring A in the quinolizine starting material to give a


B
A
N
NC
CN
(i)
FVP
(207)
(217)
Conditions :-
(i) 800°C / p = 0·005 mm Hg
(218)
(219)
1,5-H-shift.
(210B)
(210A)

Scheme 37.

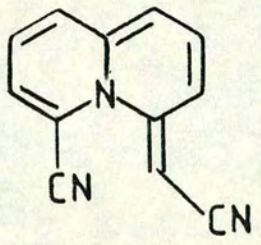
ketene species (217). This species could then undergo bond rotation followed by electrocyclic ring-closure at C-3 of the pyridine ring. The structure that resulted, (219), could then rearomatise by hydrogen migration to give the observed quinoline derivative.

The formation of the other products is less easily explained but it seems possible that FVP2 might originate by migration (mechanism obscure) of a cyano-group in the starting material (207) to C-6 of the quinolizine system. Rearrangement of the product (220) according to Scheme 38 would then give FVP2.

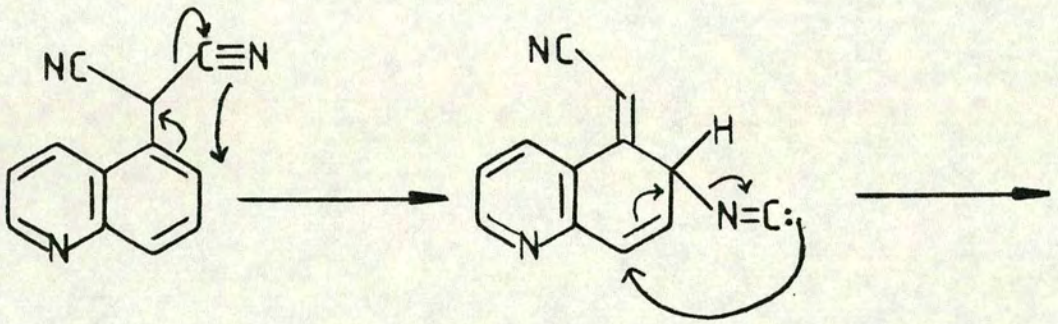
The origin of FVP1B is even more obscure but FVP1A might arise from a cyano group migration in FVP3. It is envisaged that this would occur in two stages, both of which would be [2,3]sigmatropic shifts (Scheme 38), the intermediate (221) being an isonitrile.

Clearly, these suggestions are highly speculative and leave a number of questions of detail unanswered.

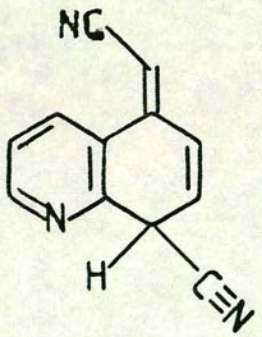
In an attempt to obtain further information concerning this type of rearrangement, 6-methylquinolizin-4-ylidene-malononitrile (223) was subjected to flash vacuum pyrolysis but extensive decomposition was noted and no characterisable product was isolated. When the quinolizinylidenecyano-acetate (23b) was subjected to fvp at 800°C and 0.005 mmHg in place of the corresponding malonitrile derivative (207), the only product (71%) was the 2-cyano[2.3.3]cyclazin-1-one (26c) previously obtained[6] in lower yield (60%) by heating the same precursor in boiling nitrobenzene.



(220)



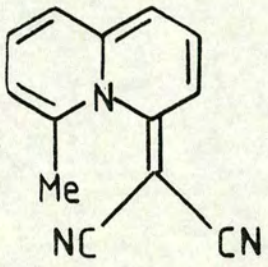
(210B) (221)



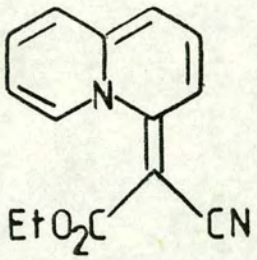
(222)

H-shift. (214)

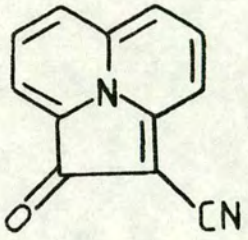
Scheme 38.



(223)



(23b)

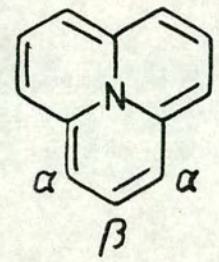


(26c)

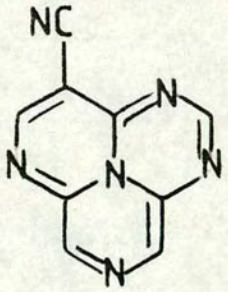
It is difficult to propose a mechanism for this fvp process, but it seems likely that it does not proceed via the mechanism previously suggested[6] for the solution process (see section 2.2.1; Introduction) since such a mechanism would involve gas phase ions.

5.2.2 Attempts to generate 2-Aza[3.3.3]cyclazines

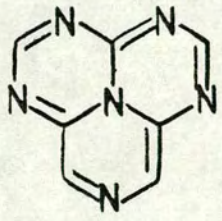
Whereas aza-substituents in the α-positions of the [3.3.3]cyclazine ring periphery are known to stabilise the molecule, aza-substituents in the β-position are predicted to have a destabilising effect. However, only



(3)



(224)

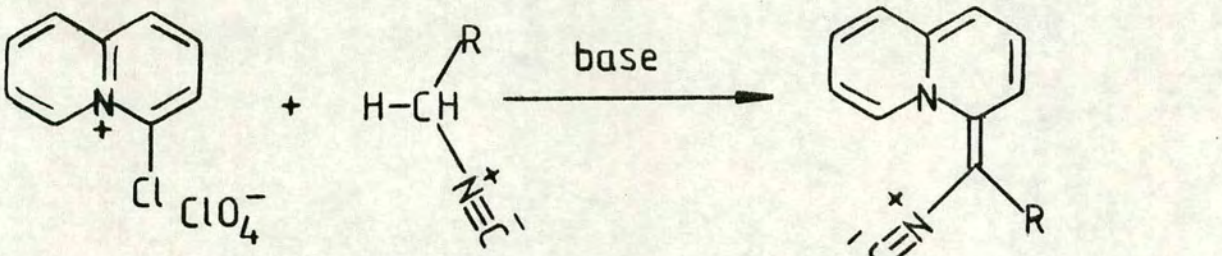


(225)

two β-aza[3.3.3]cyclazines, (224) and (225), are known[79] and here the number of stabilising α-substituents is probably more than sufficient to compensate for any destabilisation by the one β-nitrogen.

A possible approach to less highly substituted 2-aza[3.3.3]cyclazines is outlined in Scheme 39, and involves a thermally-induced electrocyclisation of a quinolizin-4-ylidene derivative (228) bearing an isocyano-group at the exocyclic carbon.

However, attempts to generate the quinolizin-4-ylidene species (228) met with little success when the electron-withdrawing group (R) was either ethoxycarbonyl or _para_-tolylsulphonyl. When the carbanions derived from ethyl isocyanoacetate (226) or _p_-tolylsulphonylmethyl isocyanide [TosMIC] (227) were allowed to react, at a low temperature, with 4-chloroquinolizinylium perchlorate (44), a red or purple colour, perhaps indicative of the intermediates (228), was produced initially but, during the course of allowing the reaction mixture to warm to room temperature, extensive decomposition (darkening) took place, accompanied by multiple product formation, and no characterisable products could be isolated.

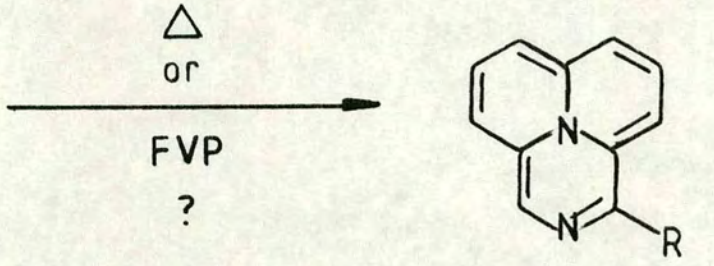


(44) (226) R = CO_2Et.

(227) R = SO_2-C_6H_4Me.

(228) a: R = CO_2Et

(228) b: R = $SO_2C_6H_4Me$.



(229 a and b)

Scheme 39.

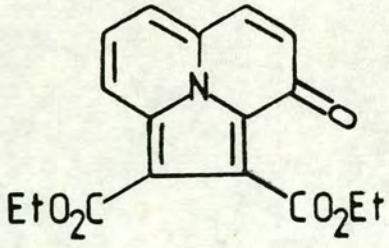
SECTION 6

6. Preparation of [2.3.3]cyclazinones

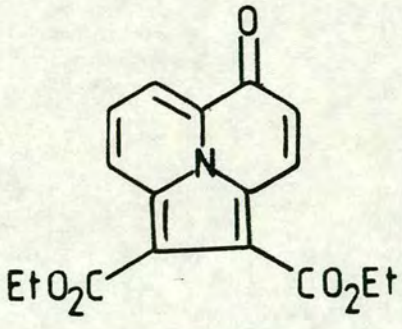
6.1 Introduction

The work described in this section arose out of the need to obtain authentic specimens of the [2.3.3]cyclazinones (181) and (183) for comparison with oxidation products of the [3.3.3]cyclazine diester (47) (see section 4.3.1).

The dimethyl ester corresponding to the di(ethoxycarbonyl)cyclazin-3-one (183) had been obtained previously[6] (section 2.2.2) by reaction of 3-hydroxyquinolizinylium[80] bromide (31) with sodium carbonate and dimethyl acetylenedicarboxylate, in boiling nitrobenzene. The synthesis of the corresponding diethyl ester was therefore expected to be straightforward. On the other hand, only a monoethoxycarbonyl derivative (182) of [2.3.3]cyclazine-5-one was



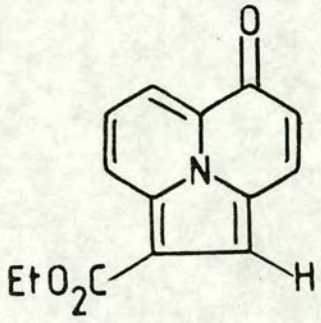
(183)



(181)

known[6] and this had been obtained in very low yield by a lengthy route involving nucleophilic substitution of a

[2.3.3]cyclazinylium salt (section 2.3, Introduction).



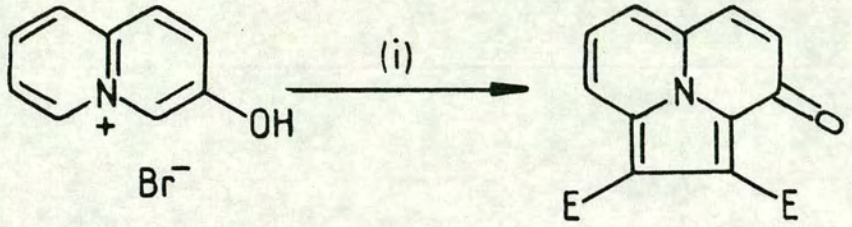
(182)

6.2 Synthesis of the di(ethoxycarbonyl)[2.3.3]cyclazin-3-one and 5-ones

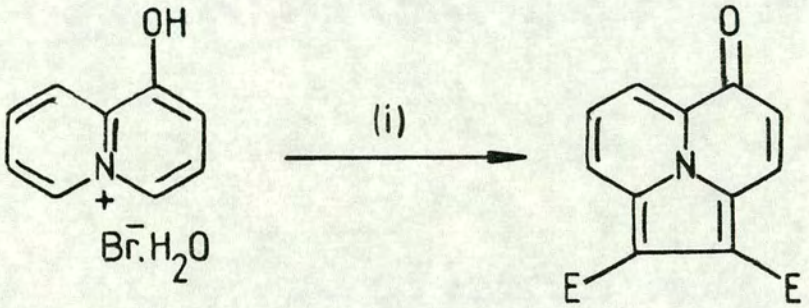
Previous experience in the preparation of [3.3.3]-cyclazines (section 2.3/Discussion) has shown that better yields of a cleaner product could be obtained by dehydrogenation with 9,10-phenanthraquinone rather than with boiling nitrobenzene. It was decided therefore, to investigate the use of this reagent in the synthesis of [2.3.3]cyclazinones.

Accordingly, the reaction of diethyl acetylene-dicarboxylate with 3-hydroxyquinolizinylium bromide[80] and anhydrous sodium carbonate was carried out in the presence of 9,10-phenanthraquinone (101) in refluxing acetonitrile. Flash chromatographic work-up gave the desired 1,2-di(ethoxycarbonyl)-3H-[2.3.3]cyclazin-3-one (183) in a 39% yield which was essentially the same as that (41%) reported[6] for the corresponding dimethyl

ester. The use of phenanthraquinone in place of nitrobenzene had not improved the yield but the reaction mixture was much cleaner and the product easier to purify. The ^{1}H n.m.r. spectrum of this diethyl ester (Table 16) was essentially the same, in the aromatic region, as that of the dimethyl ester, and was identical with that of one of the fluorescent oxidation products of the [3.3.3]cyclazine (47). (Scheme 40).



(31) (183)



(232) (181)

Reagents :-

(i) $EtO_2C-C\equiv C-CO_2Et$ / MeCN / 9,10-Phenanthraquinone / N_2 / reflux/ - Na_2CO_3.

Scheme 40.

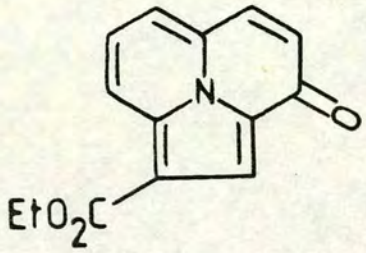
When the same procedure was applied to the reaction of 1-hydroxyquinolizinylium bromide[81] (232) with diethyl acetylenedicarboxylate, the required 1,2-di(ethoxycarbonyl)-5H-[2.3.3]cyclazin-5-one (181) was obtained in a 32% yield. This latter [2.3.3]cyclazinone was identical in all respects with the other fluorescent material obtained by the oxidation of the [3.3.3]cyclazine derivative (47).

The above syntheses thus confirmed the structures of the oxidation products as expected (Table 16).

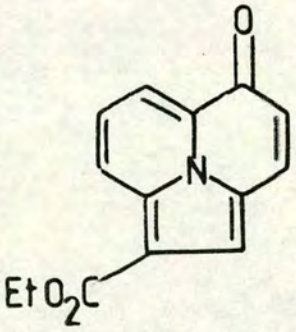
6.3 Reactions of 1- and 3-hydroxyquinolizinylium salts with ethyl propiolate in the presence of phenanthraquinone

In view of the success of these cycloaddition experiments using diethyl acetylenedicarboxylate in the presence of 9,10-phenanthraquinone, it seemed appropriate to extend the investigation by trying the same reactions with ethyl propiolate as the alkyne substrate. This type of reaction was expected to give rise to the monosubstituted [2.3.3]cyclazinones (33a) and (182), both of which have been synthesised previously[6].

When ethyl propiolate was refluxed with 3-hydroxyquinolizinylium bromide (31) in acetonitrile in the presence of 9,10-phenanthraquinone and sodium carbonate, the 1-(ethoxycarbonyl)-3H-[2.3.3]cyclazin-3-one (33a) was obtained in a 79% yield. The spectroscopic and other physical details were as observed previously[6]. This modified procedure shows a 4% increase in yield over



(33a)



(182)

the previous synthesis, and also has the advantage of being a much cleaner reaction than that found in nitrobenzene at 210°C.

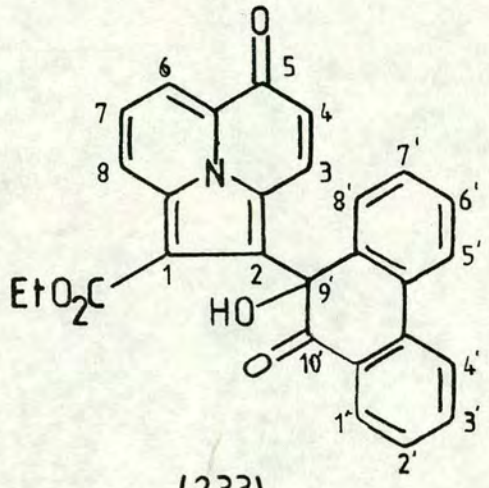
The same procedure applied to the 1-hydroxyquinolizinylium salt (232) was not as straightforward, and gave a complex mixture of products that were difficult to separate. Three products were finally isolated in low yield by a chromatographic technique described in the experimental section. One of these products (3% yield) was the expected 1-(ethoxycarbonyl)-5H-[2.3.3]cyclazin-5-one (182) as shown by comparison of its proton n.m.r. spectrum and other spectroscopic and physical data with those reported previously[6].

Both of the other two products were yellow and their mass spectra showed molecular ions at m/z 449, which corresponds in a formal sense, to 1:1-adducts of the ethoxycarbonylcyclazinone (182) with phenanthraquinone. These products will be designated CPQ(A) (9% yield) and CPQ(B) (1% yield). Their proton n.m.r. spectra showed the following features in common, though there were

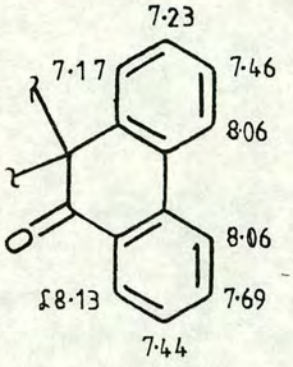
differences in chemical shifts between one compound and the other (see tables 24A and 25A); (a) an AB and an AMX spin system corresponding closely to those in the spectrum of the cyclazin-5-one (182), were easily identifiable and showed the presence of this ring system in both compounds; (b) the singlet corresponding to H-2 in the cyclazinone (182) was absent, showing that this position was occupied by a substituent; (c) eight other proton signals in the aromatic region showed complex splitting and were identified, by decoupling experiments, as belonging to two independent four-spin systems, thus indicating the presence of a substructure containing two non-equivalent ortho-di-substituted benzene rings, presumably derived from phenanthraquinone; (d) the CH_2 proton signals of the ethyl ester were non-equivalent (diastereotopic) (J_{gem} 10.9 Hz), showing that a chiral centre was present in both molecules.

In addition to these features, the major product, CPQ(A), showed an OH stretching band at 3200 cm^{-1} in its infra-red spectrum, and the OH proton n.m.r. signal was identified as a broad singlet (δ4.6) which was removed by shaking the sample with D_2O. Taken together, the foregoing spectroscopic features suggested the structure (233) for CPQ (A) and this structure was in full accord with the ^{13}C n.m.r. spectrum (Table 24B), which showed only one coincidence (of two quaternary sp^2C resonances). The aryl ketone (C=O) resonance was present at δ194.1 and the quaternary $sp^3C(OH)$ resonance at δ78.0.

Table 24A ^{1}H n.m.r. data for compound (233)



(233)



(233A)

δ[a]	m	No. of H	Results of decoupling expts.[c]										Assignment
8.83	dd	1H	hν	+				+					H-8
8.55	dd	1H	+	hν	d)			+					H-6
8.50	d	1H		d)	hν							+	H-3
8.13	dd	1H				hν	d)		+				H-1'
8.06	2xbr.d.	2H				d)	hν		+	?			H-4'/5'
7.91	dd	1H	+	+	?			hν					H-7
7.69	dt	1H				+	+		hν				H-3'
7.46	dt	1H					+			+	?		H-6'
7.44	dt	1H				+			+				H-2'
7.23	dt	1H					+			hν	?		H-7'
7.17	dd	1H								?	hν		H-8'
6.97	d	1H			+							hν	H-4
4.61[b]	br.s	1H											OH
4.08	dq	1H											>CH-H ester
4.01	dq	1H											>CH-H ester
1.07	t	3H											CH_3 ester

Coupling constants: $J_{3,4}$ 10.2; $J_{6,7}$ 7.7; $J_{6,8}$ 1.2; $J_{7,8}$ 8.5; J_{vic} 7.1; J_{gem} 10.8 Hz

a) 360 MHz in $CDCl_3$

b) Peak removed on D_2O shake

c) Decoupling experiments; hν indicates irradiation frequency: + indicates definite positive effect; ? indicates possible effect (very small)

d) Indicates collapse of signal caused by close proximity to irradiation point.

Table 24B. ^{13}C n.m.r. data for (233)

δ[a]	Peaks in DEPT Spectrum		Assignment
	pϕ= $\pi/2$[b]	pϕ= $3\pi/4$[c]	
13.9		+	sp^3CH_3
60.8		-	sp^3CH_2
78.0			sp^3COH
110.3			sp^2C
118.4	+	+	sp^2CH
122.2			sp^2C
123.2	+	+	sp^2CH
123.7	+	+	sp^2CH
123.8	+	+	sp^2CH
124.6	+	+	sp^2CH
126.6	+	+	sp^2CH
128.5			sp^2C
128.7	+	+	sp^2CH
128.8	+	+	"
129.0	+	+	"
129.4	+	+	"
129.5	+	+	"
130.3			sp^2C
132.6	+	+	sp^2CH
133.7			sp^2C
134.6	+	+	sp^2CH
136.3			sp^2C
137.7			2 x sp^2C[d]
140.1			sp^2C
163.6			sp^2C=O (ester)
175.7			sp^2C=O (cyclazine C-5)
194.1			sp^2C=O Ar'<u>C</u>=O

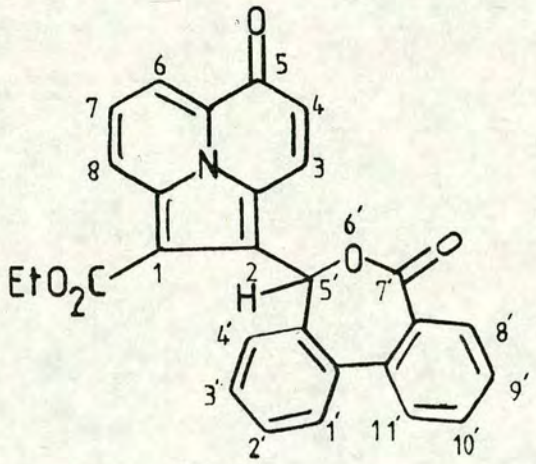
a) At 90.56 MHz in $CDCl_3$

b) CH only (+)

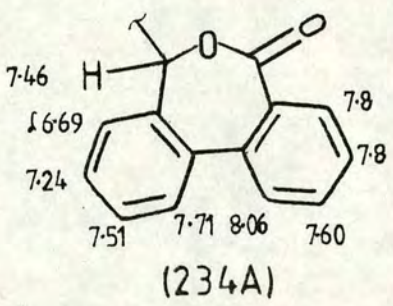
c) CH_3/CH (+ve); CH_2 (-ve); no quaternaries

d) Separated lines visible from expansion of ^{13}C n.m.r. region.

Table 25A ^{1}H n.m.r. data for compound (234)



(234)



(234A)

δ /ppm.

δ[a),b)]	m	No. of H	Results of decoupling expts.[c)]									NOE expts.[e)]		Assignment
8.93	dd	1H	hv	d)	+	+								H-8
8.85	d	1H	d)	hv			+						1%	H-3
8.63	dd	1H	+		hv	+								H-6
8.06	ddd	1H				d)		hv	+					H-11'
7.98	dd	1H	+		+	hv		d)						H-7
7.73-7.80	m	2H						+	+					H-8'/9'
7.71	dd	1H								+	+			H-1'
7.60	ddd	1H						+	hv	d)				H-10'
7.51	td	1H							d)	hv	+	+	hv	H-2'
7.46	s	1H										2%		H-5'
7.24	td	1H					d)		?	+	hv	+		H-3'
7.16	d	1H		+			hv				d)			H-4
6.69	dd	1H								+	+	hv	?	H-4'
4.11	dq	1H												CH-H(ester)
4.10	dq	1H										6.8%		CH-H(ester)
0.95	t	3H										hv		CH_3 (ester)

Coupling constants: $J_{3,4}$ 10.1; $J_{6,7}$ 7.7; $J_{6,8}$ 1.2; $J_{7,8}$ 8.5; J_{vic} 7.1; J_{gem} 10.8 Hz

a) 360 MHz spectrum in $CDCl_3$.

b) No change in spectrum when D_2O shake performed.

c) Decoupling experiments; hv indicates irradiation frequency; + indicates definite positive effect; ? indicates possible effect (very small).

d) Indicates collapse of signal caused by close proximity to irradiation point.

e) N.O.E. experiments; hv indicates irradiation frequency; % enhancements given.

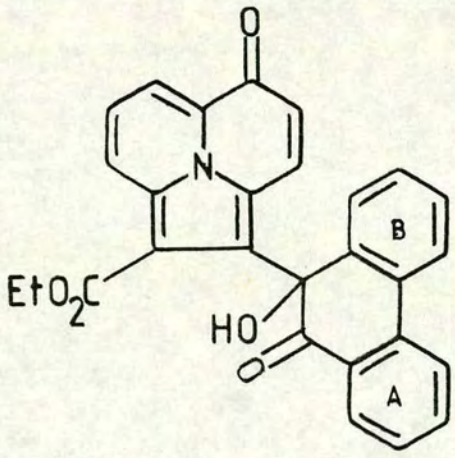
Table 25B ^{13}C n.m.r. data for compound (234)

δ [a)]	Peaks in DEPT Spectrum		Assignment
	$p\phi = \pi/2$ [b)]	$p\phi = 3\pi/4$ [c)]	
13.6		+	$sp^3 CH_3$
60.5		-	$sp^3 CH_2$
75.6	+	+	sp^3 <u>C</u>H-O
109.1			sp^2 C
118.7	+	+	sp^2 CH
120.7			sp^2 C
123.8	+	+	sp^2 CH
125.2	+	+	"
125.6	+	+	"
126.9	+	+	"
128.6	+	+	"
128.7	+	+	"
128.9	+	+	"
129.0	+	+	"
129.8	+	+	"
130.1			sp^2 C
131.3			"
131.7	+	+	sp^2 CH
132.9	+	+	"
133.0	+	+	"
133.7			sp^2 C
137.3			"
137.4			"
138.0			"
138.2			"
163.2			sp^2 C=O (ester)
168.8			sp^2 C=O (lactone)
175.9			sp^2 C=O (cyclazine C-5)

a) AT 90.56 MHz in $CDCl_3$

b) CH only +ve

c) CH/CH_3 (+ve); CH_2 (-ve); no quaternaries.

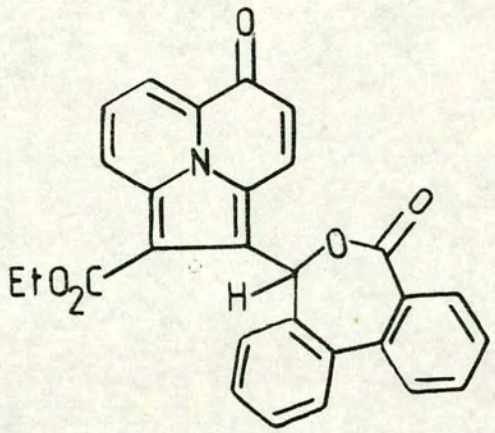


(233)
CPQ[A]

In contrast to CPQ(A), the minor product, CPQ(B), showed no evidence for the presence of a hydroxyl group. Its ^{1}H n.m.r. spectrum contained a sharp singlet at δ7.46, not removed by D_2O, which was at first thought to be due to a proton joined to an sp^2-carbon. However, the thirteen sp^2-CH resonances observable in the ^{13}C n.m.r. spectrum [Table 25B] were fully accounted for by association with the 5 cyclazine and 8 benzenoid proton signals leaving an sp^3-CH resonance at δ75.6 as the only peak that could be associated with the sharp proton singlet. These features pointed to the presence of a highly deshielded proton environment such as $Ar_2\underline{CH}$-O-. The ^{13}C spectrum of CPQ(B) differed further from that of CPQ(A) in containing an additional ester (or lactone) carbonyl peak at δ168.8 instead of the aryl ketone peak. Confirmation of the presence of an additional ester

group was obtained from the i.r. spectrum which showed a carbonyl band at 1720 cm^{-1}, not present in the spectrum of CPQ(A).

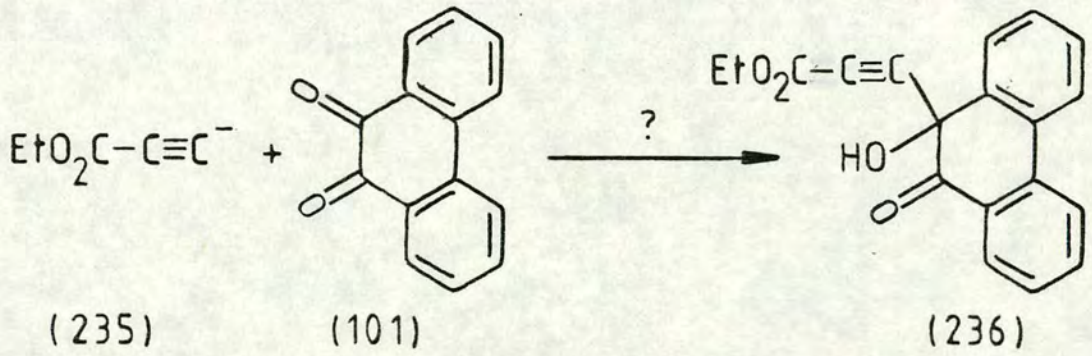
The only structure for CPQ(B) that is consistent with all the spectroscopic evidence is that shown in formula (234). Additional evidence for this structure

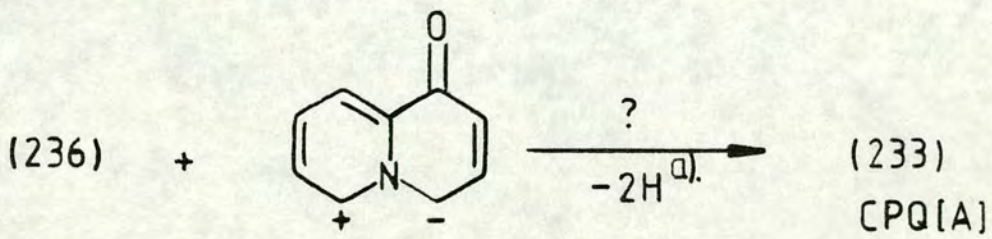


(234)
CPQ[B]

was sought from the nuclear Overhauser effect using the method of difference spectroscopy (NOEDS). Irradiation of the sharp proton singlet at δ7.46 caused a very small enhancement (~ 1%) of the H-3 resonance of the cyclazine ring system; and an even smaller enhancement of a benzenoid proton resonance at δ6.7 (presumably due to H-4'). Less expectedly, irradiation of the CH_3 triplet of the ethyl ester group caused a small enhancement (~ 2%) of the δ7.46 signal as well as a larger (~ 7%) enhancement of one of the diastereotpic CH_2 proton signals.

The mechanism for the formation of CPQ(A) and CPQ(B) is not clear, since it involves the cyclazine moiety becoming joined to a phenanthraquinone derived moiety. One possibility considered was reaction of an ethyl propiolate anion with phenanthraquinone, followed by cycloaddition of the resulting adduct (236) to the hydroxyquinolizinylium betaine (237) [Scheme 41].





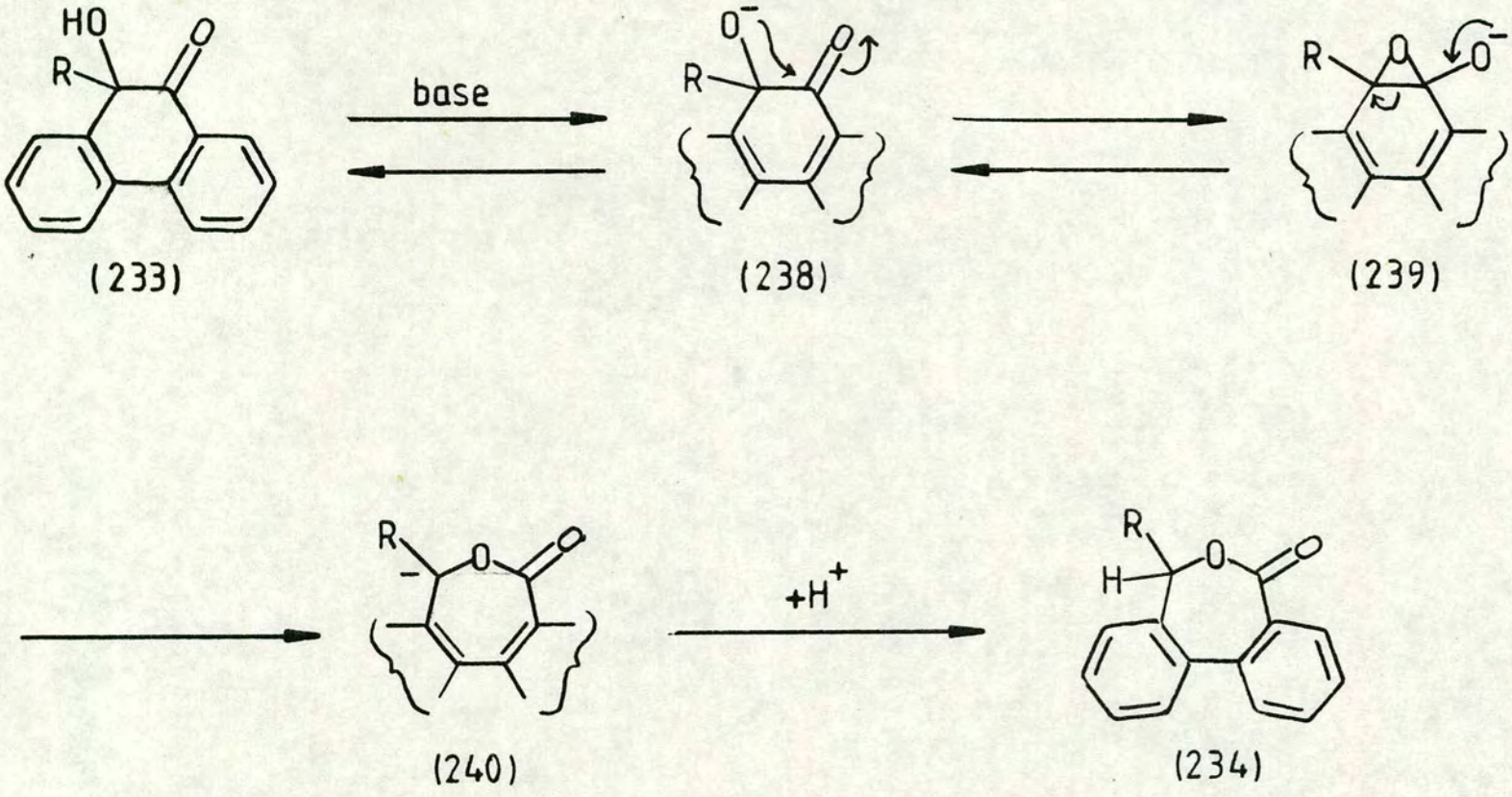
(237)

a). Dehydrogenation.

Scheme 41.

However, experiments with phenanthraquinone and ethyl propiolate under the conditions of the cyclazine preparation gave no evidence for the formation of such an adduct. Likewise, reaction of 1-ethoxycarbonyl-5H-[2.3.3]cyclazin-5-one (182) with 9,10-phenanthraquinone (101) in the presence of a base also failed to give either CPQ(A) or

CPQ(B) after six hours refluxing in acetonitrile. Experimentally CPQ(A) (233) was converted partially into CPQ(B) (234) during six hours in refluxing acetonitrile in the presence of anhydrous sodium carbonate, thus revealing the probable origin of CPQ(B). A mechanism for the rearrangement of the hydroxyketone structure to the lactone structure can be formulated as shown in Scheme 42, but no precedent for such a rearrangement in aromatic hydroxyketones has been found.



(233) (238) (239) (240) (234)

Scheme 42.

SECTION III

EXPERIMENTAL

Instrumentation and General Techniques

Melting points of new compounds were obtained on a Kofler (Reichert) hot-stage microscope and are not corrected.

Microanalyses for carbon, hydrogen and nitrogen were carried out on a Carlo-Erba elemental analyser operated by Mrs. E. McDougall.

Infrared spectra were recorded on Perkin-Elmer 781 or 271 spectrophotometers. Solids were run as nujol mulls and liquids as thin films on sodium chloride plates. Characteristic peaks are given and spectra were calibrated with the polystyrene peak at 1603 cm^{-1}.

Proton (^{1}H) nuclear magnetic resonance spectra were recorded on a Varian EM360 spectrometer (operating at 60 MHz) for routine analyses, and on a Bruker WP-80 instrument (operating at 80 MHz) or a Bruker WP-200 instrument (operating at 200 MHz) by Mr. J.R.A. Millar; Mr. L.H. Bell and Mr. K. Shaw. High resolution and decoupled spectra were obtained on a Bruker WH-360 instrument (operating at 360 MHz) operated by Dr. I.H. Sadler and Dr. D. Reed. Chemical shift values were recorded on the δ scale in p.p.m. relative to tetramethylsilane as internal standard (δ = 0) or chloroform (δ = 7.25). Unless otherwise noted, the solvent used was deuteriochloroform.

Carbon (^{13}C) nuclear magnetic resonance spectra were obtained at 50.32 MHz on a Bruker WP-200 machine or at 90.56 MHz on a Bruker WH-360 machine.

Mass spectra and exact mass measurements were recorded on either an A.E.I. MS902 spectrometer or a Kratos MS50 spectrometer by Mr. A. Taylor or Miss E. Stevenson. The parent ion ($M^{+\cdot}$) is given.

Ultraviolet and visible spectra were recorded on a Pye-Unicam SP-8 400 spectrophotometer. The abbreviations 'sh' and 'i' refer to a shoulder on the curve and a point of inflexion respectively.

Alumina used for column chromatography was either Laporte Industries, Type UG or Fluka neutral, Type 507C. The alumina was deactivated by shaking it with water (eg. 10% deact. from 90 g of fully-activated alumina and 10 g of deionised water). Silica for column chromatography was Merck Kieselgel 60 (230-400 mesh ASTM). For alumina thin layer chromatography, analytical (50 x 200 mm) and preparative (200 x 200 mm) plates were of 0.3 and 1.0 mm thick coverings respectively. T.l.c. alumnia was Merck, Aluminium oxide 60G, type E or Fluka Type G (10 % gypsum). For silica thin layer chromatography, both analytical and preparative plates were 0.5 mm thick and were of Merck Kieselgel G or Fluka Kieselgel GF254 types with premixed fluorescent indicators. The components were observed under ultraviolet light or by their reaction with iodine vapour.

Organic solutions were dried by standing over anhydrous magnesium sulphate for a minimum of one hour and were evaporated under reduced pressure on a rotary evaporator.

Commercially available solvents were used without

further purification unless otherwise indicated. Where pure methanol, ethanol, acetone or ether, the commercial Analytical Reagent (A.R.) grade solvent was used. Dry acetonitrile, dimethylformamide, diisopropylamine and nitrobenzene were prepared by storing over freshly activated molecular sieve (type 4A, Fisons). Dry ether and toluene were prepared by addition of sodium wire to the solvent. Dry tetrahydrofuran was prepared by either heating under reflux with calcium hydride in an atmosphere of dry nitrogen for 3 h and then distilling on to freshly activated molecular sieve or alternatively by refluxing it for 3 h with sodium metal pieces again under a nitrogen atmosphere with benzophenone present to indicate dryness and lack of peroxides. Once again the dried THF was distilled onto freshly activated molecular sieve (type 4A). Dimethoxyethane (DME) was similarly dried over calcium hydride. Light petroleum refers to the redistilled 40-60°C boiling fraction and was used for both chromatography and recrystallisation. Distilled and dried ethyl acetate was used to remove compounds from the stationary phase during preparative t.l.c. work-ups. Ether refers to diethylether.

During much of this experimental work, oxygen-free conditions were employed. Air-sensitive liquids (eg. butyl-lithium solution in n-hexane) were stored and transferred under oxygen-free dry nitrogen according to the techniques described by Brown[85]. Reaction flasks and storage vessels for reagents were equipped with rubber septa through which

reagents, solvents, and solutions were transferred using a hypodermic syringe or double-ended needle.

A slight positive pressure of oxygen-free nitrogen was maintained in the reaction vessel, excess nitrogen being allowed to escape through a liquid paraffin bubbler.

Abbreviations and Symbols

b.p.	boiling points
m.p.	melting points
t.l.c.	thin layer chromatography
n.m.r.	nuclear magnetic resonance
^{1}H	proton n.m.r.
^{13}C	carbon-13 n.m.r.
s; d; t;	singlet; doublet; triplet;
q; m	quartet; multiplet
quat	quaternary carbon
J	coupling constant
δ	chemical shift
p.p.m.	parts per million
br.	broad
$\bar{\nu}$	wavenumber (cm^{-1})
$M^{+\cdot}$	mass of molecular ion
m/z	mass to charge ratio
h; min	hours; minutes
M	mol cm^{-3}
u.v.	ultra violet
sh; i	shoulder; inflexion

E2 Investigation of a novel route to [3.3.3]cyclazine derivatives

E2.2 Reaction of 4-chloroquinolizinylium perchlorate with diethyl glutaconate: A new route to dihydro[3.3.3]cyclazines

Preparation of starting materials

(a) 4H-Quinolizin-4-one

This compound was prepared by a variation of the procedure of Bohlmann and his co-workers[82].

Sodium (0.85 g, 0.04 mol) was dissolved in absolute ethanol (25 ml), and to the stirred solution were added chilled solutions of freshly distilled ethyl 2-pyridyl acetate (17.00 g, 0.10 mol) in ethanol (40 mol) and diethyl ethoxymethylenemalonate (27.20 g, 0.12 mol) in ethanol (40 ml) at 0°C. Stirring was continued at this temperature for 0.5 h prior to allowing the mixture to stand at room temperature for 24 h. At this stage, the reaction mixture was quenched with water (170 ml) with vigorous stirring, and the yellow-green precipitate that resulted was filtered off, washed with ice cold portions of ethanol and ether and then air-dried to give 1,3-di(ethoxycarbonyl)-4H-quinolizin-4-one (25.80 g, 89%).

4H-Quinolizin-4-one was prepared from the above 1,3-di(ethoxycarbonyl)-4H-quinolizin-4-one in 87% yield (after vacuum distillation) by the method of Boekelheide and Lodge[83], b.p. 90-100°C/0.05 mmHg (lit.[83] m.p. 71-72°C;

lit. b.p. 134-138°C/0.7 mmHg)[84].

(b) 4-Chloroquinolizinylium perchlorate

The title compound was prepared according to the method of Van Allan and Reynolds[49].

Starting from 4H-quinolizin-4-one (11.00 g), the perchlorate (18.40 g, 81%) was obtained as colourless crystals, infrared spectrum identical with that of an authentic specimen.

E2.2.1 Identification of the products

Under a dry nitrogen atmosphere, the sodium salt of diethyl glutaconate was produced by reaction of the ester (0.45 g, 2.4 mmol) with sodium hydride (0.12 g [2.4 mmol] of a 50% mineral oil dispersion) in dry THF (20 ml) at room temperature. 4-Chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was added at 0°C in small aliquots, and the stirred mixture was allowed to come to room temperature, when the solution changed from an initial clear yellow colour to an orange-red colour. Further stirring at room temperature (2 h) followed by heating to 55-60°C for 0.5 h gave rise to a purple coloured solution which, by analytical t.l.c., was shown to contain at least four components. The solution was concentrated and subjected to medium pressure liquid chromatography (m.p.l.c.) on alumina (6% deactivated). Elution with light petroleum (b.p. 40-60°C)-dichloromethane gave the following results.

(i) A yellow-green band yielded diethyl pyrido[2,1,6-de]-quinolizine-1,3-dicarboxylate [(47a)] (typically 2%) as brown-purple needles, m.p. 145-146°C (from light petroleum) (lit[22] m.p. 145-146°C). The ^{1}H n.m.r. spectrum of this

compound was identical with that reported previously[22].

(ii) A purple band yielded diethyl 3a,4-dihydropyrido-[2,1,6-de]quinolizine-1,3-dicarboxylate [(49)] (typically 15%) as dark blue prisms, m.p. 99-100°C (from light petroleum) (lit[22] m.p. 99-100°C). The ^{1}H n.m.r. spectrum of this compound was identical with that reported previously] ^{1}H/Table 1; ^{13}C/Table 1A].

(iii) An orange band yielded slightly impure diethyl 3a,6-dihydropyrido[2,1,6-de]quinolizine-1,3-dicarboxylate (89) as an orange oil (5%), which was unstable and converted readily into the two compounds isolated above. The ^{1}H n.m.r. spectrum is described in the text and the data are given in Table 2.

Further elution of the m.p.l.c. column with ethanol removed a purple-red band that gave a slightly unstable red-brown solid. This compound was recrystallised from light petroleum (b.p. 60-80°C) - ethyl acetate to give dark red prisms (8%), m.p. 201-204°C (Found: M^+ 626.2628. $C_{36}H_{38}N_2O_8$ requires M^+ 626.2628); $\bar{\nu}_{max}$ 1690, 1670, 1645 (C=O) cm^{-1}; ^{1}H n.m.r. (Table 3). This compound was tentatively formulated as a (4+2)π Diels-Alder dimer (91) as discussed in section 2.2.1 of the text.

E2.2.2 Optimised procedure for the synthesis of dihydro[3.3.3]cyclazines (LDA procedure)[38]

The techniques employed[85] during this part of the synthetic work are described briefly in the introduction to the experimental section.

A dry 3-necked round-bottomed flask (50 ml) equipped

with a condenser, rubber septum and liquid paraffin bubbler was flushed with dry nitrogen, and charged with diisopropylamine (0.25 g, 2.5 mmol) in dry THF (2 ml). This solution was cooled to -5 to -10°C, and n-butyl-lithium (2.5 mmol) was added dropwise with stirring. After 5 min. the solution was cooled to -78°C and diethyl glutaconate (0.45 g, 2.4 mmol) in dry THF (15 ml) was added. The colourless clear solution became yellow and, after 20 min. at -78°C, 4-chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was added in small aliquots whilst maintaining the low temperature. The solution was allowed to warm to room temperature slowly, stirred for a further 2.5 h, and refluxed under nitrogen for 0.5 h. The solution was then cooled, filtered and loaded onto a flash column (alumina, 6% deactivated/neutral) and the column was eluted with dichloromethane and ethyl acetate. Removal of a broad purple band and evaporation of the solvent in vacuo, gave the dihydro mixture (>50%) as a purple oil.

E2.3 Dehydrogenation of the dihydro[3.3.3]cyclazines

Testing of reagents for dehydrogenation

A mixture of dihydrocyclazines was prepared by the procedure described in section E2.2.2. Portions of the mixture were treated with potential dehydrogenating reagents in small scale reactions which were monitored by t.l.c. (SiO_2-CH_2Cl_2 or CH_2Cl_2-Et_2O). In promising cases, the reaction was scaled up and the dehydrogenation

Table 26.

Reagent (equiv.)	Solvent	Other additives	Temp/ °C	Time/ h	Result[a]
$PhNO_2$ (excess)	$PhNO_2$	K_2CO_3	210°	0.2	15%
σ-chloranil (1.2-1.8)	DMF, THF, CH_2Cl_2 or EtOAc		R.T.	0.3-0.75	≤2%
DDQ (1.1)	DMF, THF, or CH_2Cl_2		R.T.		Traces (47a)
TTC[b] (1.5)	MeCN		81°	1.25	≤15%
TTC[b] (1.5)	MeCN	K_2CO_3	81°	1.5	15%
TTC[b] (1.5)	Pyridine		114°	0.7-1.0	13-25%
TTC[b] (1.5)	Pyridine	K_2CO_3	114°	0.75	50%
Ph_3CBF_4[c] (1.0-1.5)	MeCN	Pyridine or MS[d]	R.T. or 114°	1.5-24	Traces (47a)
MnO_2 (10.0)[e]	MeCN		R.T.	72	Traces (47a) and 6,6'-bi-cyclazinyl (74)
Pd-C (1.0)[e]	THF		67°		oxidation products
NiO_2 (1.0)[e]	CH_2Cl_2		R.T.		oxidation products

a) % yields refer to the cyclazine diester (47a) isolated in the larger scale reactions

b) 2,3,5-triphenyltetrazolium chloride

c) Trityl tetrafluoroborate (ref. 42)

d) Powdered Linde molecular sieve, type 5A

e) w/w ratio

product (47a) was isolated by chromatography on alumina (column or preparative t.l.c.). A selection of the many reactions carried out is summarised in the following table [Table 26, see separate page].

Purification of 9,10-phenanthraquinone

Pure phenanthraquinone was obtained by the procedure of Vogel[86] from 80% technical grade material (Aldrich).

9,10-Phenanthraquinone was obtained as orange needles from glacial acetic acid, m.p. 209-211°C (lit. m.p. 209-211°C (Aldrich chemical catalogue)).

Use of 9,10-phenanthraquinone as a dehydrogenating reagent for the isolated mixture of dihydrocyclazines

A mixture of dihydro[3.3.3]cyclazines was prepared by the procedure described in section E2.2.2. The mixture (0.6 g, 2.0 mmol) was then refluxed with 9,10-phenanthraquinone (0.47 g, 2.2 mmol) in dry THF (40 ml) for 3 h under a dry nitrogen atmosphere. A excess (0.5 ml) of trimethyl phosphite was added to the hot solution which was then stirred and allowed to cool over a period of 1 h. The solvent was removed in vacuo, and the purple residue chromatographed on alumina (10% deactivated; neutral). Elution with light petroleum (b.p. 40-60°C)-toluene removed a yellow-green band that gave a crude purple solid. Recrystallisation of this solid from cyclohexane-THF gave diethyl pyrido-[2,1,6-de]quinolizine-1,3-dicarboxylate 52%; based on the initial amount of 4-chloroquinolizinylium perchlorate. The yield for the dehydrogenation step was estimated as about 70% based on the initial quantity of

dihydrocyclazine mixture.

E2.4 "One-pot" synthesis of 1,3-di(ethoxycarbonyl)[3.3.3]-cyclazine

Under a dry nitrogen atmosphere, diethyl glutaconate (0.45 g, 2.4 mmol) in THF (15 ml) was added at -78°C to LDA (2.5 mmol) prepared as described in section E2.2.2 in THF (2 ml) and the mixture was stirred at this temperature for 20 min. Whilst maintaining the temperature at -78°C, 4-chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was added in small aliquots. After the addition was complete, the reaction mixture was stirred for 0.5 h, allowed to come to room temperature, and kept for a further 1 h. 9,10-Phenanthraquinone (0.53 g, 2.5 mmol) was then added and the mixture was refluxed, under nitrogen, for 3 h [reaction checked for completion by t.l.c. on silica in CH_2Cl_2-Et_2O (4:1)]. Trimethyl phosphite (0.6 ml, excess) was then added and the stirred solution was cooled slowly over a period of 1 h.

The reaction mixture was filtered and the filtrate was subjected to flash column chromatography (on neutral alumina, 6% deactivated), eluting with dichloromethane-ether. A green-yellow band was removed that gave a purple solid. Recrystallisation of this solid from cyclohexane-THF gave diethyl pyrido-[2,1,6-de]quinolizine-1,3-dicarboxylate as purple-brown needles, m.p. 144-146°C (lit.[22] m.p. 146-147°C), $\bar{\nu}_{max}$ 1655 cm^{-1}, identical in all respects with the product reported[22] previously.

The yield obtained by this procedure were typically

in the range 55-60% but, on a number of occasions, small scale reactions gave even better yields, rising in one individual experiment to 83%.

E2.5 Synthesis of other [3.3.3]cyclazine derivatives

β-Hydroxyglutaronitrile (1,3-dicyanopropan - 2-ol)

This compound was prepared by the method of Johnson, Panella et al[46a].

Starting from epichlorohydrin (102.00 g, 1.10 mol), β-hydroxyglutaronitrile was obtained as a clear pale yellow liquid (61.0 g, 60%), b.p. 150-160°C/0.2 mmHg (lit.[46] b.p. 155-160°C/0.4 mmHg); $\bar{\nu}_{max}$ 3450 (OH), 2260 (C≡N) cm^{-1}.

Note:

(i) Even when this material was stored in the refrigerator it rapidly darkened to a brown colour but was easily repurified, when required, by Kügelrohr distillation.

3-Acetoxyglutaronitrile

This compound was prepared by the method of Johnson, Panella, Carlson and Hunneman[46b].

Starting from β-hydroxyglutaronitrile (7.65 g), the acetoxy compound was obtained (7.98 g, 75%) as a slightly pink liquid, b.p. 95-100°C/0.05 mmHg (lit.[46] 126.5°C/ 1.0 mmHg); $\bar{\nu}$max 2250 (C≡N), 1740 (C=O) cm^{-1}; δ_H (60 MHz) 2.1 (S, 3H), 2.8 (d, 4H), 5.2 (q, 1H).

Glutacononitrile (1,3-dicyanopropene)

The title compound was synthesised as a mixture of E- and Z- isomers in 74% yield by flash vacuum pyrolysis of 3-acetoxyglutaronitrile.

The acetoxy-compound (3.60 g) was slowly vapourised through a silica pyrolysis tube at 700°C/0.05 mmHg and the product was collected in a trap cooled by liquid nitrogen. After warming to room temperature, the trap contained a brown liquid which was dissolved in ether and the resulting solution was washed with aqueous sodium bicarbonate (3 x 75 ml). The aqueous phase was adjusted to pH 8 and further extracted with chloroform. The combined organic phases were dried and evaporated to give crude glutacononitrile as a clear yellow oil. The oil was distilled in a Kügelrohr to give glutacononitrile (1,3-dicyanopropene) as a clear colourless liquid, b.p. 75°C/0.05 mmHg (lit.[46b] b.p. 84-86°C/0.35 mmHg for E/Z-isomer mixture; $\bar{\nu}$max 2260/2230 (C≡N), 1642 (C=C) cm^{-1}; δ_H (60 MHz) 3.4 (dd, 2H, CH_2-trans), 3.5 (dd, 2H, CH_2-cis), 5.8 (dd, 1H, =C<u>H</u>-CN, trans), 5.9 (dd, 1H, =C<u>H</u>-CN, cis), 6.2-6.6 (dt, 1H, -C<u>H</u>=, cis), 6.7 (dt, -C<u>H</u>=, trans).

<u>1,3-Dicyano-3a,4-dihydropyrido[2,1,6-de]quinolizine</u> (108)

Under a dry nitrogen atmosphere, freshly distilled glutacononitrile (E/Z-mixture) [0.23 g, 2.5 mmol] dissolved in dry THF (18 ml) was added to a solution of LDA (2.5 mmol) in dry THF (2 ml) at -78°C. After 20 min. stirring at this temperature, 4-chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was added carefully in small portions, whilst maintaining the low temperature. The yellow colour of the glutacononitrile anion gave way to orange-red and then purple. The solution was allowed to warm to room temperature before being refluxed for 2 h. After this

time, the solution was cooled, filtered and then loaded on to a flash column of alumina (neutral, 10% deactivated). Elution with dichloromethane and ethyl acetate gave the following results.

(i) A purple band yielded a purple solid that was recrystallised from light petroleum (b.p. 60-80°C/toluene to give 1,3-dicyano-3a,4-dihydropyrido[2,1,6-de]quinolizine (108) (0.12 g, 27%) as purple prisms, m.p. 245-248°C [Note] (Found: C, 76.4; H, 4.1; N, 19.1. $C_{14}H_9N_3$ requires C, 76.7; H, 4.1; N, 19.2%); $\bar{\nu}$max 2190/2180 (C≡N) cm^{-1}; δ_H (200 MHz) Table 4; m/z 219($M^{+\cdot}$), 218 (100%), 192, 165, 109.5 (M^{2+}).

Note: During the melting point determination a possible change of crystal structure was noted at 178°C, and a m.p. at 273°C. This may correspond to conversion of the dihydro-compound into the fully unsaturated 1,3-dicyano[3.3.3]cyclazine derivative (lit.[22] m.p. 270-273°C)

(ii) A purple-orange band yielded a dark red solid that was shown by t.l.c. (silica-CH_2Cl_2) to be a mixture of at least four components. The crude solid was redissolved in chloroform, and the solution was washed with water (2 x 50 ml), dried and evaporated. Preparative t.l.c. (silica/CH_2Cl_2:Et_2O (10:1)) of the residue gave a major red band from which was recovered a red solid. Recrystallisation from light petroleum (b.p. 60-80°C)-ethyl acetate gave 2-(quinolizin-4'-ylidene)-4-cyano-5-(cyanomethyl)hept-3-ene-1,7-dinitrile (109) (0.018 g, 2%) as red prisms,

m.p. 200°C (Found: M^+ 311.1172. $C_{19}H_{13}N_5$ requires M^+ 311.1171); $\bar{\nu}$max 2145 (C≡N) cm^{-1}; δ_H and δ_C Table 6.

1,3-Dicyanopyrido[2,1,6-de]quinolizine (104)

The foregoing dihydro[3.3.3]cyclazine (0.120 g, 0.5 mmol) was refluxed in dry toluene (15 ml) with a slight excess of 9,10-phenanthraquinone (0.125 g, 0.6 mmol) under dry nitrogen. After 1 h, the solution was cooled and the solvent was removed in vacuo. Flash column chromatography of the residue on alumina (10% deactivated, neutral) in toluene-dichloromethane gave the following results.

(i) 9,10-phenanthraquinone (29%) was recovered.

(ii) A yellow-green band yielded a purple-brown solid that was recrystallised from acetonitrile to give 1,3-dicyanopyrido[2,1,6-de]quinolizine (104) (0.046 g, 38%) [11% yield from 4-chloroquinolizinylium perchlorate], as purple-brown needles, m.p. 269-271°C (lit.[22] m.p. 270-273°C); $\bar{\nu}$max 2190 (C≡N) cm^{-1}; δ_H (d^6-dmso) Table 5. The m.p. and n.m.r. data are consistent with those published previously[22].

Further elution with ether-ethyl acetate gave a trace amount of a red solid which was not characterised.

Ethyl 4-cyanobut-2-enoate

This compound was prepared by a procedure adapted from the work of Supniewski and Salzberg[87a] and of Rietz[87b] on the preparation of allylic cyanides.

Copper(I) cyanide (2.85 g, 0.03 mol) [Note 1] and potassium iodide (0.1 g, 0.6 mmol) were stirred and heated at 110-120°C with ethyl 4-bromocrotonate (5.71 g, 0.03 mol) under a dry nitrogen atmosphere. After 48 h, dry ether

(60 ml) was added, and the slurry was filtered and evaporated [Note 2] to give a yellow-brown oil. Distillation of the oil gave a clear pale yellow liquid (1.94 g), b.p. 75-100°C/18 mmHg, $\bar{\nu}$max 2250/2220 (C≡N), 1770/1720 (C=O) cm^{-1}, δ_H (80 MHz) 1.08 (t, 3H, CH_3), 1.09 (t, 3H, CH_3), 1.10 (t, 3H, CH_3), 3.1 (dd, 2H, J 7.1/1.7 Hz, CH_2), 3.21 (d, 2H, J 1.7 Hz, CH_2), 3.28 (dd, 2H, J 7.1/1.7 Hz, CH_2), 3,97 (q, 2H, CH_2), 3.99 (q, 2H, CH_2), 4.00 (q, 2H, CH_2), 5.2-5.6 (m, 1H, J=13.6 Hz, C<u>H</u>=CH(CO_2Et)), 6.98 (dt, 1H, J=15.6/1.8 Hz, -C<u>H</u>=CH-CH_2-/ trans), 6.3-6.9 (m, 1H, CH=C<u>H</u>-CH_2, cis), plus other obscure peaks [Note 3].

<u>Note 1</u>: The CuCN was dried at 110°C for 16 h.

<u>Note 2</u>: Solvent was evaporated <u>in vacuo</u> at low water bath temperature to prevent loss of product.

<u>Note 3</u>: The n.m.r. spectrum was complex, showing the presence of at least 3 components including the <u>cis</u> and <u>trans</u> forms of the desired compound.

<u>Ethyl 3-cyanopyrido[2,1,6-de]quinolizine-1-carboxylate</u> (112)

Under a dry nitrogen atmosphere, the foregoing impure sample of ethyl 4-cyanobut-2-enoate (0.35 g, 2.5 mmol) dissolved in dry THF (16 ml) was added to a solution of LDA (2.5 mmol) in dry THF (2 ml) at -78°C. After 20 min. stirring at this low temperature, 4-chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was added in small aliquots whilst maintaining the low temperature. The solution colour changed from yellow via orange-red to purple, as is typical for these dihydrocyclazine syntheses. The

reaction mixture was then warmed to room temperature and refluxed for 1.5 h. Subsequently, the mixture was cooled and subjected to flash column chromatography (alumina, neutral). Elution with dichloromethane-ethyl acetate removed a purple band from which was obtained the dihydrocyclazine (113) (mixture of isomers) as a deep purple crystalline solid (0.20 g, 38%) which was not purified further nor fully characterised. [m.p. 125-135°C (isomer mixture), (Found: $M^{+\cdot}$ 266. $C_{16}H_{14}N_2O_2$ requires $M^{+\cdot}$ 266), $\bar{\nu}$max 2180 (C≡N), 1665 (C=O) cm^{-1}; m/z 266 ($M^{+\cdot}$), 237 (100%, $M^{+\cdot}$ -HCN)]. This product was refluxed with 9,10-phenanthraquinone (0.26 g, 1.2 mmol) in dry THF (20 ml) under dry nitrogen. After 4 h, dehydrogenation was incomplete (t.l.c.) and the reflux temperature was increased by evaporating the solvent and replacing it with toluene (20 ml). Refluxing was continued (0.75 h) until t.l.c [silica/CH_2Cl-Et_2O (4:1)] indicated that no dihydrocompound (purple spot) remained.

At this stage, trimethyl phosphite (0.2 ml, excess) was added, and the solution was stirred under N_2 for 0.5 h. Evaporation of the solvent and chromatography by m.p.l.c. on alumina (Fluka neutral, 10% deactivated), eluting with various combinations of light petroleum (b.p. 40-60°C)-toluene-dichloromethane-ether, gave a yellow-brown band that yielded a purple crystalline solid. Recrystallisation from cyclohexane-ethyl acetate gave ethyl 3-cyanopyrido-[2,1,6-de]quinolizine-1-carboxylate (112) [0.107 g, 52%; or 20% based on 4-chloroquinolizinylium perchlorate]

as purple needles, m.p. 183-186°C (Found: C, 72.8; H, 4.6; N, 10.7. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.6; N, 10.6%); $\bar{\nu}$max 2190 (C≡N), 1680 (C=O) cm^{-1}; δ_H and δ_C Table 7; m/z 264 ($M^{+\cdot}$), 236 (100%).

N-(2,4-Dinitrophenyl)pyridinium chloride

The title compound was prepared by the method of Zincke[88].

Starting from 1-chloro-2,4-dinitrobenzene (40.5 g, 0.2 mol), the N-(2,4-dinitrophenyl)pyridinium chloride was obtained as colourless prisms (48.7 g, 87%) from ethanol.

Glutacondialdehyde (sodium salt dihydrate)

This salt was prepared by the method of Becher[47].

Starting from the foregoing pyridinium chloride (25.0 g, 0.09 mol), glutacondialdehyde was prepared as its sodium salt dihydrate (4.20 g, 39%), a yellow solid. Its structure was confirmed by infrared and ^1H n.m.r. spectroscopy: $\bar{\nu}$max 3380 (H_2O), 1715 (C=O), 1670 (C=C) cm^{-1}; δ_H (d^6-dmso) [60 MHz] 3.4 (br.s, (H_2O), 5.2 (dd, 2H, H-2/4), 7.1 (t, 1H, H-3), 8.6 (d, 2H, H-1/5).

Reaction of glutacondialdehyde sodium salt dihydrate with 4-chloroquinolizinylium perchlorate

(a) In acetonitrile

The foregoing glutacondialdehyde salt (0.030 g, 0.2 mmol) was stirred with 4-chloroquinolizinylium perchlorate (0.052 g, 0.2 mmol) in acetonitrile (1 ml) under a nitrogen atmosphere. Analytical t.l.c. (silica/Et_2O or ethyl acetate) was used to monitor any reaction. After 5 h

stirring, t.l.c. revealed only weak spots of very low chromatographic mobility, which were not consistent with the presence of a cyclazine or dihydrocyclazine. Thus, no work-up was performed for this particular reaction.

(b) In dimethylformamide

To an ice-cold solution of the sodium salt of glutacondialdehyde (0.030 g, 0.2 mmol) in DMF (1 ml) was added 4-chloroquinolizinylium perchlorate (0.052 g, 2 mmol). The solution was stirred vigorously under N_2 before being allowed to warm slowly to room temperature. Subsequent stirring at r.t. for 24 h, followed by removal of the DMF in vacuo gave an oily residue. This residue was taken up in water (20 ml) and extracted with chloroform (3 x 50 ml), and the organic phase resulting was washed with water and dried. Evaporation of the solvent gave a dark brown oil that was shown by analytical t.l.c. (silica-ethyl acetate) to contain at least five components (low yield) which from their low chromatographic mobilities (Rf) did not appear to be [3.3.3]cyclazine derivatives. No separation was performed and no definite conclusions may be drawn.

1,3-Di(p-tolylsulphonyl)propene

This material was obtained by the procedure of Mikhailova, Yurevich and Bulat[48].

Starting from p-tolyl 3-bromo-1-propenyl sulphone (3.60 g, 0.013 mol), the title compound was obtained (3.06 g, 68%) as a colourless crystalline solid (from ethanol) m.p. 153-156°C (lit.[48] m.p. 154-155°C);

$\bar{\nu}$max 1580 (C=C), 1315/1305 (SO_2), 1155/1145 (SO_2) cm^{-1}; δ_H (80 MHz) δ2.37 (s, 3H, Me), 2.43 (s, 3H, Me), 3.87 (d, 2H, CH_2, J 7.3 Hz), 6.30 (d, 1H, CH=C<u>H</u>-SO_2, J 15.2 Hz), 6.73 (dt, 1H, CH_2-C<u>H</u>=CH, J 15.1/7.4 Hz), 7.1-7.4 (m, 4H, aromatic H), 7.5-7.7 (m, 4H, aromatic H); m/z 350 ($M^{+\cdot}$).

<u>Reaction of 1,3-di(p-tolylsulphonyl)propene with 4-chloroquinolizinylium perchlorate</u>

(a) <u>LDA as the base</u>

The procedure described in section E2.2.2 was used to generate the anion of the propene derivative (0.88 g, 2.5 mmol). After addition of the quinolizinylium salt, the solution was refluxed for 1.5 h, cooled and passed through a column of alumina (neutral, 10% deactivated) to remove baseline materials. The purple oil obtained from the eluate was then subjected to m.p.l.c. on alumina (neutral, 10% deactivated), eluting first with toluene-dichloromethane and then with ether. The following fractions were obtained.

(i) A pinkish-purple band on the column gave a pale purple solid which was identified as starting propene (0.20 g recovered) with a faint coloured impurity. It is possible that the purple colouration could have been due to a trace of the 3a,4-dihydro[3.3.3]cyclazine derivative [δ_H 3.1, 4.7].

(ii) An orange band on the column gave a dark red solid (0.012 g) that was not characterised further because of its lack of purity (by t.l.c.).

Thus, no definite conclusions may be drawn from this experiment.

(b) Butyl-lithium as the base

In these experiments, butyl-lithium was used directly with the propene derivative to ensure complete formation of the anion of the disulphonylpropene.

1,3-Di(p-tolylsulphonyl)propene (0.88 g, 2.5 mmol) was dissolved in dry THF (20 ml) under a dry N_2 atmosphere. The flask was cooled to -78°C and butyl-lithium (5.0 mmol) was added dropwise with stirring. This gave rise to a clear red solution after complete addition. Then, whilst maintaining the temperature at - 78°C, 4-chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was added in small portions. The mixture was stirred at - 78°C for 0.5 h, and then allowed to warm to room temperature. Any reaction was followed by analytical t.l.c. [silica-CH_2Cl_2:Et_2O (10:1)]. The mixture was then stirred and refluxed for 2 h, cooled and subjected to column chromatography on alumina (neutral, 10% deactivated). Elution with dichloromethane-ethyl acetate yielded two fractions: (A) a purple solid (0.13 g) and (B) a purple-red solid (0.34 g). T.l.c. of fraction (A) showed several components, including an orange, a purple and a yellow spot which resembled other [3.3.3]cyclazines and dihydrocyclazines in their chromatographic mobility. This isolated material also contained starting propene. Recrystallisation of this crude material yielded mainly starting material (disulphonylpropene) and evaporation of the mother liquor gave a purple oil (0.17 g). Preparative t.l.c. (silica - 5% ether in CH_2Cl_2) of the oil gave

three bands as detailed below.

(a) A yellow band yielding a small amount of a yellow-brown solid which was unstable and rapidly converted into a dark brown oil. This fraction was not analysed further.

(b) A purple band yielding a purple-pink solid (0.009 g). In view of the very low yield, this material was not analysed further.

(c) An orange band yielding an orange-red solid (0.009 g). Spectroscopic data were obtained but the product could not be identified.

The spectroscopic data (i.r., m.s., ^{1}H n.m.r.) for fraction (B) from the column were also uninformative.

Similar results were obtained when this experiment was repeated with the propene derivative and butyl-lithium in equimolar ratio.

To summarise, the low yields of these materials and the lack of stability of some of them led to difficulties in their characterisation, and only tentative conclusions may be drawn from these experiments.

1,2,3-Tri(methoxycarbonyl)prop-1-ene[Trimethyl aconitate]

The title compound was synthesised from a technical mixture of itaconic and aconitic acids (15/85%) using a general esterification technique[86].

The aconitic acid mixture (12.0 g, 0.05 mol of aconitic acid) was refluxed with methanol (30 ml) and conc. sulphuric acid (0.5 g) for seven hours before the cooled mixture was poured carefully into water (100 ml), and the aqueous phase was extracted with ether (100 ml).

The organic layer was washed with aqueous sodium hydrogen carbonate and then dried over magnesium sulphate. Distillation under reduced pressure gave the triester (6.38 g, 63%) as a colourless liquid, b.p. 111-112°C/ 0.38 mmHg (lit.[89] b.p. 161°C/14 mmHg; 270°C); $\bar{\nu}$max 1745br (C=O), 1730br (C=O), 1655 (C=C) cm^{-1}; δ_H (80 MHz) 3.43 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.69 (d, 2H, CH_2, J 0.9 Hz), 6.67 (d, 1H, C<u>H</u>= , J = 0.9 Hz).

<u>Reaction of 1,2,3-tri(methoxycarbonyl)prop-1-ene with 4-chloroquinolizinylium perchlorate</u>

Under a dry nitrogen atmosphere, LDA (2.5 mmol) was generated[38] at -5°C in dry THF (4 ml). The flask was then cooled to -78°C and 1,2,3-tri(methoxycarbonyl)propene (0.52 g, 2.5 mmol) was added in THF (16 ml). This gave rise to a clear red solution on stirring. 4-Chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was then added at -78°C in small aliquots, and the solution was allowed to come to room temperature, which gave rise to a clear green colour. T.l.c. analysis [silica/CH_2Cl_2-Et_2O (4:1) or ethyl acetate] revealed only chromatographically immobile material. The mixture was then heated to 55-60°C for 2 h, cooled and filtered. A black solid (0.31 g), retained on the filter, was washed with dichloromethane and shown (i.r. and ^1H n.m.r.) to be an impure specimen of the starting quinolizinylium salt (<u>ca</u>. 60% recovery).

The organic filtrate and washings were evaporated <u>in vacuo</u> to give a very small amount of brown residue,

which showed only a baseline smear on t.l.c., together with some minor spots visible in u.v. light (λ 365 nm). A proton n.m.r. spectrum of this residue gave no distinct information.

Dimethyl 2-methylpyrido[2,1,6-de]quinolizine-1,3-dicarboxylate (126)

The title compound was synthesised by the "one-pot" procedure described in section E2.4.

LDA (2.5 mmol) was generated at -5°C in THF (2 ml) under a dry nitrogen atmosphere. After cooling the stirred solution to -78°C, freshly distilled dimethyl 3-methyl-glutaconate (0.43 g, 2.5 mmol) in dry THF (15 ml) was added, giving a pale yellow solution. Whilst maintaining the temperature at -78°C, 4-chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was added in small aliquots, causing a colour change, first to orange and then to green. After 0.75 h at -78°C, the stirred solution was allowed to come to room temperature, prior to addition of 9,10-phenanthraquinone (0.53 g, 2.5 mmol) and refluxing for 2.5 h. Trimethyl phosphite (0.6 ml, excess) was added to the hot solution which was then stirred and cooled slowly under N_2. Filtration and evaporation of the filtrate gave a dark green oil, which was subjected to flash chromatography on alumina (neutral, 6% deactivated). Elution with dichloromethane gave a yellow-orange band which yielded a purple oily solid. This oily material was kept in a desiccator at 0.05 mmHg for 3 h to remove any traces of trimethyl phosphite. Recrystallisation [Note 1]

from cyclohexane-THF gave dimethyl 2-methylpyrido [2,1,6-de]-quinolizine-1,3-dicarboxylate (126) [0.20 g, 34%] as purple needles, m.p. dec 122-124°C (Found: C, 68.2; H, 5.0; N, 4.9; M^+ 297.0999. $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%; M^+ 297.1001); $\bar{\nu}$max 1690/1670 (C=O) cm^{-1}; λ_{max} (EtOH) 259i, 290, 338 sh, 410, 446i and 470 nm ($\log_{10}\varepsilon$ 4.06, 4.36, 3.41, 4.07, 4.13, and 4.30), δ_H [200 MHz] Table 8 (Text); [Note 2].

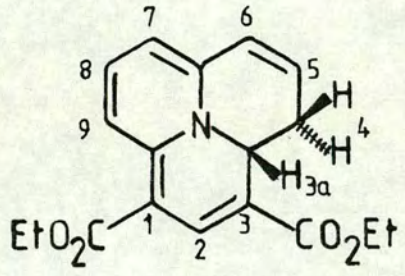
Further elution of the column with dichloromethane-ether-ethyl acetate gave a green band that yielded a green solid (0.18 g) which could not be purified further and appeared to contain more than one component by t.l.c. (silica/EtOAc or alumina/EtOAc). Its infrared spectrum showed a broad peak at $\bar{\nu}$max 1710 cm^{-1}, but no attempt was made to characterise this material which was probably polymeric.

Notes

[1] Careful recrystallisation, avoiding a long period of heating, was necessary to avoid decomposition.

[2] The cyclazine derivative was apparently unstable on both silica and alumina stationary phases and could only be observed when in high concentration. Thus losses during chromatography must have been substantial.

Table 1. (200 MHz) ^{1}H n.m.r. spectrum of 3a,4-Dihydro--1,3-(diethoxycarbonyl)-[3.3.3]cyclazine (Diethyl-3a,4-dihydro-pyrido[2,1,6-de]quinolizine-1,3-dicarboxylate) [49]



(49)

^{1}H n.m.r. ($CDCl_3$)

δ	m	(H)	J/Hz	assign
1.29	t	3H	J=7.11 Hz	CH_3(ester)
1.30	t	3H	J=7.06	CH_3(ester)
2.36	qt	1H	J=18.08/11.5/2/2	H-4'
3.34	ddd	1H	J=18.08/7.05/2.40	H-4
4.18	2 x q (overlap)	4H	J=7.10	2 x CH_2 ester
5.55	dd	1H	J=11.73/2.37	H-3A
6.30	2 x "d"(overlap)	2H	J indet.	H-6/H-7
6.62	ddd	1H	J=9.38/7.10/2.24	H-5
7.21	dd	1H	J=9.21/6.90	H-8
7.89	s	1H		H-2
8.70	dd	1H	J=9.29/1.20	H-9

$J_{8,9}$ = 9.3 Hz; $J_{7,8}$ = 6.9; $J_{7,9}$ = 1.2 Hz; $J_{5,6}$ = 9.4 Hz;

$J_{3a,4}$ = 2.4 (cis); $J_{3a,4'}$ = 11.6 (trans); $J_{4,4'}$ = 18.1 (gem);

$J_{4,5}$ = 7.1 ; $J_{4',5}$ = 2.2 Hz

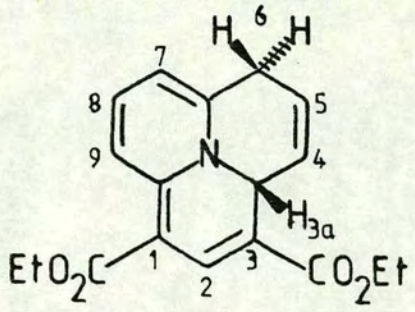
Table 1A. ^{13}C n.m.r. spectrum of compound (49)

δ [a] /$CDCl_3$	DEPT ($p\phi = 3\pi/4$) [b] /assign	
14.28	CH_3 (ester)	
14.49	CH_3 "	
33.52	CH_2 (C-4)	
58.81	CH_2 (ester)	
59.37	CH_2 (ester)	
60.95	CH (C-3a)	
87.56	$>C=$ (C-1 or 3)	
105.52	$>C=$ (C-1 or 3)	
113.21	CH	C 2/5/6/7/8 and 9
121.77	CH	
124.43	CH	
136.22	CH	
136.82	CH	
139.93	CH	
144.37	$>C=$	C_{6A} and C_{9A} (α to N)
150.25	$>C=$	
165.80	$>C=O$	ester
166.20	$>C=O$	

a) fully decoupled spectrum (WP-200 , 50.32 MHz)

b) CH_3 / CH ↑ ; CH_2 ↓

Table 2. [1]H n.m.r. spectrum of 3a,6-Dihydro-1,3-(diethoxycarbonyl)-[3.3.3]cyclazine (Diethyl-3a,4-dihydropyrido[2,1,6-de]quinolizine-1,3-dicarboxylate) [89]



(89)

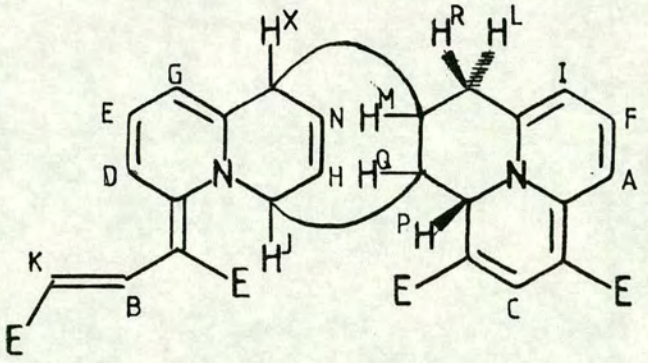
[1]H n.m.r.[a)]/$CDCl_3$

δ	m	(H)	J/Hz	assign
δ1.29	t	3H	7.10	CH_3 (ester)
δ1.31	t	3H	7.10	CH_3 (ester)
δ3.41	m	2H	J indeterminate	H-6,6'
δ4.18	q	2H	J = 7.08	CH_2 (ester)
δ4.20	q	2H	J = 7.07	CH_2 (ester)
δ5.18	qd or ddd	1H	J = 3.42/2.40/0.79	H-3a
δ6.12	d(dt)	1H	J = 9.26/4.28/2.40	H-5
δ6.37	qt	1H	J = 9.26/3.42/1.33	H-4
δ6.43	qt	1H	J = 6.93/1.37/0.90	H-7
δ7.22	dd	1H	J = 9.22/6.93	H-8
δ8.00	d	1H	J = 0.79	H-2
δ8.57	dd	1H	J = 9.22/1.37	H-9

$J_{8,9}$ = 9.2 Hz; $J_{7,8}$ = 6.9; $J_{7,9}$ = 1.4; $J_{4,5}$ = 9.3; $J_{2,3a}$ = 0.8; $J_{3a,4}$ = 3.42; $J_{3a,5}$ = 2.4; $J_{5,6}$ = 4.3; $J_{4,6}$ = 1.33 (allylic); $J_{6,7}$ = 0.90 (allylic)

a) In $CDCl_3$ at 200MHz.

Table 3. ^{1}H n.m.r. spectrum [200 MHz] of compound (91)



E = CO_2Et.

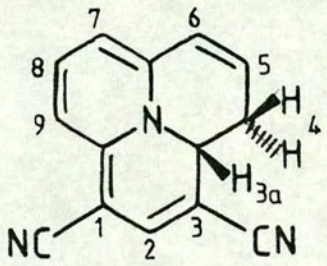
(91)

δH_{CDCl_3}	m	(H)	J/Hz[b]	assign
δ1.22	t	3H	J=7.10	CH_3 (ester)
δ1.26	t	3H	"	"
δ1.29	t	3H	"	"
δ1.30	t	3H	"	"
δ2.62	d	1H	$J_{L,R}$=16.0 Hz	R
δ2.76	m or ddd?	1H	J indeterminate	M
δ3.22	dt?	1H	$J_{Q,M}$=10.3, $J_{Q,M} \approx J_{Q,P} \approx$3 Hz	Q
δ3.25	dd	1H	$J_{L,R}$=16 Hz, $J_{L,M}$=7.1	L
δ4.0-4.3	m	9H	J indet.	X + $\underline{CH_2}$-CH_3
	(includ. ester CH_2 peaks)			
δ5.26	d	1H	$J_{B,K}$=15.1	K
δ5.76	d	1H	$J_{P,Q}$=3.3	P
δ5.83	ddd[a]	1H	$J_{H,J} \approx$5.7, $J_{J,Q} \approx$3, $J_{J,N} \approx$1.5	J
δ6.16	ddd	1H	$J_{H,N}$=7.5, $J_{N,X} \approx$6, $J_{N,J} \approx$1.5	N
δ6.20	d	1H	$J_{I,F}$=6.8 Hz	I
δ6.58	ddd	1H	$J_{H,N}$=7.5, $J_{H,J}$=5.7, $J_{H,X} \approx$1.5 Hz	H
δ6.87	dd	1H	$J_{C,G}$=7.1, $J_{D,G}$=1.3	G
δ7.06	dd	1H	$J_{A,F}$=9.2, $J_{I,F}$=6.8	F
δ7.47	dd	1H	$J_{D,E}$=8.5, $J_{E,G}$=7.1	E
δ7.65	dd	1H	$J_{D,E}$=8.5, $J_{D,G}$=2 Hz	D
δ7.89	s	1H		C
δ8.09	d	1H	$J_{B,K}$=15.1Hz (trans coupling)	B
δ8.62	d	1H	$J_{A,F}$=9.2 Hz	A

a) Appears as a dt

b) Coupling data from line-narrowed expansions at 200 MHz

Table 4. ^{1}H n.m.r. spectrum (200 MHz) of compound (108)



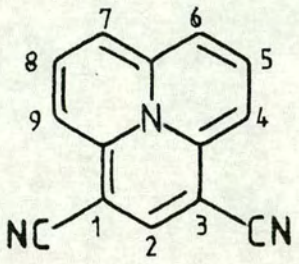
(108)

^{1}H n.m.r. ($CDCl_3$)

δ_H	m	(H)	J/Hz	assign
δ6.69	d	1H	J = 1.4	H-2
δ5.68	ddd	1H	10.7/5.4/1.4	H-3a
δ3.02	m	(2H)	J indet.	H-4,4'
δ6.40	ddd	1H	9.6/6.1/3.3	H-5
δ6.18	dd	1H	J indet.	H-6
δ6.19	dd	1H	J indet.	H-7
δ7.14	dd	1H	8.9/6.9	H-8
δ6.96	dd	1H	8.9/1.5	H-9

$J_{2,3a}$ = 1.4; $J_{8,9}$ = 8.9; $J_{7,9}$ =1.5; $J_{7,8}$ = 6.9 Hz

Table 5. ^{1}H n.m.r. spectrum [80 MHz] of (104) in d^6-dmso



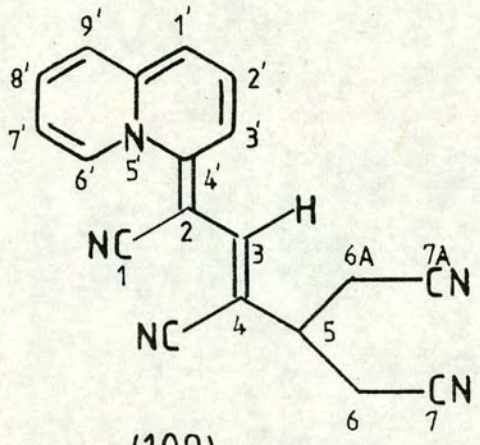
(104)

^{1}H n.m.r.

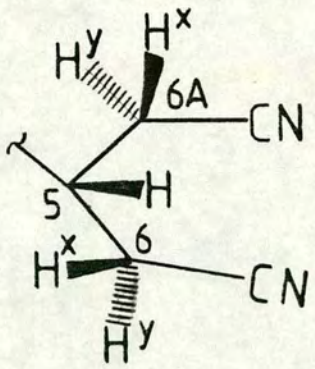
δ	m	(H)	J/Hz	assign
δ5.89	s	1H		H-2
δ5.26	dd	2H	8.4/1.4	H-4/9
δ5.10	t	2H	8.4/8.4	H-5/8
δ4.72	dd	2H	7.8/1.4	H-6/7

$J_{4,5}$ 8.4; $J_{4,6}$ 1.4; $J_{5,6}$ 8.1 Hz

Table 6. ^{1}H and ^{13}C n.m.r. spectra of (109)



(109)



(109A)

^{1}H n.m.r.[a)]

δ	m	H	J/Hz	assign
2.50	dd	2H	J_{gem} 16.80/8.81	H^{Y} -6,6A
2.63	dd	2H	16.84/6.42	H^{X} -6,6A
2.97	tt	1H	8.8/6.5	H-5
7.00	s	1H		H-3
7.69	ddd	1H	5.9/3.5/0.7	H-1'
7.78	dt	1H	7.0, 1.7	H-7'
7.94-8.01	m	3H	$J_{indet.}$	H-2', 3', 8'
8.09	ddd	1H	8.8/1.8/0.8	H-9'
8.32	dq	1H	7.2/1.0	H-6'

J_{H^X,H^Y} 16.8; J_{5,H^X} 6.4; J_{5,H^Y} 8.8; $J_{1',2'}$ 5.9; $J_{1,3}$ 3.5; $J_{1,6}$ 0.7;

$J_{6',7'} \sim J_{7',8'}$ 7.0; $J_{7',9'}$ 1.8; $J_{8',9'}$ 8.8; $J_{6',9'}$ 0.8, $J_{6',8'}$ 1.0 Hz

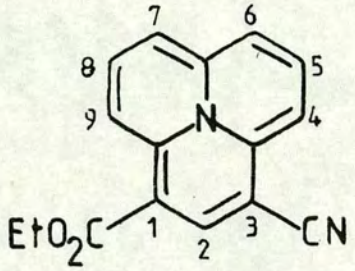
^{13}C n.m.r.[b)]

δ	assign	δ	assign
21.84	sp^3CH_2	127.71	
38.59	sp^3CH	132.39	
118.44		132.76	sp^2CH
120.55	sp^2CH	133.54	
122.43		142.50	

a) 200 MHz spectrum in $CDCl_3$

b) 50.32 MHz in d^6-acetone. DEPT ($p\phi = 3\pi/4$) only.

Table 7. ^{1}H and ^{13}C n.m.r. spectra of (112)



(112)

^{1}H n.m.r.[a)]

δ	m	(H)	J/Hz	Assign
1.14	t	3H	7.1	CH_3CH_2-
3.92	q	2H	7.1	CH_3-CH_2-
4.90	dd	1H	7.8/1.5	H-6
4.97	dd	1H	8.3/1.5	H-7
5.03	dd	1H	8.2/1.4	H-4
5.88	t	1H	8.1	H-5
5.97	t	1H	8.3	H-8
6.26	s	1H		H-2
6.50	dd	1H	8.4/1.5	H-9

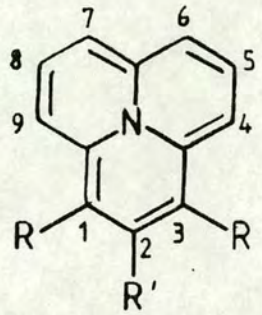
$J_{5,6}$ 7.8; $J_{4,6}$ 1.5; $J_{7,8}$ 8.3; $J_{7,9}$ 1.5; $J_{4,5}$ 8.1; $J_{8,9}$ 8.4 Hz

^{13}C n.m.r.[b)]

δ	assign		δ	assign	
14.08	sp^3CH_3		117.06	spC≡N	
59.40	sp^3CH_2		138.53	sp^2CH	C_5, C_8 & C_2
84.80	sp^2C	C_1 & C_3	139.44	sp^2CH	
102.00	sp^2C		149.69	sp^2CH	
109.16	sp^2CH	C_4 & C_9	153.99	sp^2C	C_{3A}, C_{6A} & C_{9A}
111.47	sp^2CH		154.20	sp^2C	
115.87	sp^2CH	C_6 & C_7	154.35	sp^2C	
116.20	sp^2CH		161.86	sp^2C=O	

a) 200 MHz spectrum run in $CDCl_3$ (with sodium dithionite/ D_2O shake)

Table 8. ^{1}H n.m.r. spectrum comparison of compounds (47a), (126), (127), (122) and (128)



Compound	δ/H a) H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	J/Hz
(47a) b) R=CO_2Et, R'=H	(1.18) (3.99)	7.09	(1.18) (3.99)	6.68	6.08	5.21	5.21	6.08	6.68	$J_{4,5}=J_{5,6}=8.1$ $J_{4,6}=1.7$
(126) R=CO_2Me, R'=Me	(3.51)	(1.16)	(3.51)	4.64	5.47	4.42	4.42	5.47	4.64	$J_{4,5}=J_{5,6}=8.2$ $J_{4,6}=1.3$
(127) b) R=CO_2Me, R'=Ph	(2.91)	(6.7-7.3)	(2.91)	4.99	5.57	5.54	5.54	5.57	4.99	$J_{4,5}=J_{5,6}=8$ $J_{4,6}=2$
(122) b) R=R'=CO_2Me	(3.45)	(3.60)	(3.45)	6.20	6.14	5.33	5.33	6.14	6.20	N/A
(128) b) R=CO_2Et, R'=H, 5-Me	(1.18) (4.01)	7.33	(1.18) (4.01)	6.78	(1.65)	5.24	5.31	6.16	6.76	$J_{7,8}=J_{8,9}=8.3$ $J_{4,6}=1.5$, $J_{7,9}=1.6$

a) All chemical shifts measured in $CDCl_3$/ Values in parenthesis indicate substituent groups.

b) data taken from ref. 22

E3 Investigation of a quinolizinethione as a potential precursor of a [3.3.3]cyclazine

E3.2 Attempts to prepare a 4H-quinolizine-4-thione derivative

Reaction of 1,3-di(ethoxycarbonyl)-4H-quinolizine-4-one with phosphorus pentasulphide

(a) In toluene: The quinolizinone derivative (prepared by the method outlined in section E2.2) [0.50 g, 1.7 mmol] was refluxed in dry toluene (15 ml) with phosphorus pentasulphide (0.60 g, 2.7 mmol) with exclusion of moisture. After 5 h, the reaction mixture had darkened from an initial clear yellow to an orange-brown colour. The organic phase was decanted off and the residue was leached with boiling toluene. The toluene fractions were combined and evaporated under reduced pressure to give an orange-red solid. This crude solid was subjected to flash chromatography on silica, eluting with dichloromethane-ethyl acetate, and two bands were removed:

(i) a yellow band that gave a brown solid, which was recrystallised from light petroleum (b.p. 60-80°C)-ethyl acetate to give 1-(ethoxycarbonyl)-3-(ethoxythiocarbonyl)-4H-quinolizine-4-one (142) [0.023 g, 4%] as orange-yellow prisms, m.p. 152-155°C (Found: C, 58.6; H 4.9; N, 4.5. $C_{15}H_{15}NO_4S$ requires C, 59.0; H, 4.9; N, 4.6%); $\bar{\nu}$max 1705 (C=O), 1675 (C=O), 1210 (C=S) cm^{-1}; δ_H and δ_C Tables 9 and 10; m/z 305 ($M^{+\cdot}$); and

(ii) another yellow band that gave only a trace amount of recovered starting quinolizinone.

(b) In xylene: When the above experiment was repeated in xylene, a 2% yield of the thioester (142) was obtained and some starting material was recovered (30%).

Reaction of 1,3-di(ethoxycarbonyl)-4H-quinolizin-4-one with Lawesson's reagent

Lawesson's reagent [2,4-bis(4-methoxyphenyl)--1,3-dithia-2,4-diphosphetane-2,4-disulphide] (0.40 g, 1.0 mmol) was stirred and refluxed with the 4H-quinolizin-4-one derivative (0.50 g, 1.7 mmol) in anhydrous toluene (40 ml). After 4 h [Note 1], the mixture was cooled and the solvent was removed under reduced pressure. The residues were then dissolved in dichloromethane and subjected to flash column chromatography on silica. Elution with dichloromethane-ethyl acetate gave:-

(i) a pale yellow solid (0.12 g) from a yellow band, which was shown by ^{1}H n.m.r. and m.s. to be a product, $(MeO\text{-}C_6H_4\text{-}P(S)\text{-}O)_3$ derived from Lawesson's reagent[52b], m.p. 157°C (lit.[52b] m.p. 160°C), δ_H [60 MHz] 3.9 (s, OMe), 6.8-9.2 (m, aromatic-H), 7.8-8.3 (m, aromatic-H), m/z 558 ($M^{+\cdot}$), and

(ii) a yellow solid from a brown-yellow band on the column. This solid was recrystallised from light petroleum (b.p. 60-80°C)-ethyl acetate to give 1-(ethoxycarbonyl)--3-(ethoxythiocarbonyl)-4H-4-oxo-quinolizine (142) [0.100 g, 20%] (Note 2) as orange-yellow prisms, m.p. 152-155°C, all other data identical with those of the specimen obtained from the P_2S_5 reaction, and

(iii) a yellow solid that was recrystallised from

ethanol to give the starting quinolizinone derivative (0.174 g, 35%).

[Note 1] An increase in reflux time to 8 h gave only 7% yield of the thioester, and only a trace of the starting quinolizinone derivative was recovered. More decomposition product was evident on the column.

[Note 2] The yield of thioester is 29% based on unrecovered starting material.

E3.3 Preparation of the 4H-quinolizine-4-thione derivative

Attempts to prepare 4-chloro-1,3-di(ethoxycarbonyl)-quinolizinylium perchlorate

(a) With phosphoryl chloride

This procedure was based on the preparation of 4-chloroquinolizinylium perchlorate by Van Allan and Reynolds[49].

1,3-Di(ethoxycarbonyl)quinolizin-4-one (0.50 g, 1.7 mmol) was suspended in phosphoryl chloride (0.6 ml) and heated to 90°C for 0.5 h. On cooling, a yellow solid precipitated out and this was filtered off rapidly (sintered glass filter funnel), washed with dry ether and dissolved in ethanol-water (2:1, 9 ml). Perchloric acid (60%, 0.34 g, 2.0 mmol) was added to the clear yellow solution which, upon being stirred and cooled, deposited a yellow precipitate. Further amounts of this precipitate were obtained by cooling and carefully concentrating the filtrate. Spectroscopic analysis revealed that this yellow solid was recovered quinolizin-4-one derivative

(0.4 g, 80%). No chloroquinolizinylium derivative was isolated.

(b) With oxalyl chloride

1,3-Di(ethoxycarbonyl)-4H-quinolizin-4-one (0.50 g, 1.7 mmol) was dissolved in dry chloroform (10 ml), and oxalyl chloride (0.18 ml, 2.0 mmol) was added to the stirred solution. The mixture was refluxed for 1.5 h, but analytical t.l.c. (silica-CH_2Cl_2) revealed that no reaction was occurring. The solution was worked-up by removing the solvent and the oxalyl chloride under reduced pressure and then by trituration of the remaining yellow solid. Recrystallisation from ethanol gave recovered starting quinolizinone (0.46 g, 92%).

Preparation of 1,3-di(ethoxycarbonyl)-4H-quinolizine-4-thione (133)

The procedure of Van Allan and Reynolds[49] was modified to avoid isolation of the intermediate chloroquinolizinylium salt. 1,3-Di(ethoxycarbonyl)-4H-quinolizin-4-one (0.50 g, 1.7 mmol) was dissolved in phosphoryl chloride (1.0 ml) by heating the stirred mixture to 90°C for 1 h, with exclusion of moisture from the reaction flask. Subsequent cooling and addition of dry ether (5 ml) gave a yellow precipitate which was filtered off rapidly (sintered glass funnel) and dissolved in dry DMF. To this solution was added sodium sulphide nonahydrate (1.5 g, > 5 mmol) dissolved in dry DMF (10 ml), and the mixture was stirred at room temperature. After 0.5 h, water (50 ml) was added and the solution was extracted with dichloromethane

(4 x 50 ml). The aqueous phase was neutralised with HCl and re-extracted with dichloromethane. The combined dichloromethane solution was washed once with water, dried, and evaporated to give an orange-yellow solid which was subjected to flash column chromatography on silica. Elution with dichloromethane-ethyl acetate removed two bands.

(i) An orange-yellow band on the column yielded a yellow solid which was recrystallised from light petroleum (b.p. 60-80°C)-ethyl acetate to give 1,3-di(ethoxycarbonyl)-4H-quinolizine-4-thione (133) (0.037 g, 7%, or 10% yield based on unrecovered starting quinolizinone) as golden yellow needles, m.p. 137-139°C, (Found: C, 58.6; H, 4.9; N, 4.5; M^+ 305.0721. $C_{15}H_{15}NO_4S$ requires C, 59.0; H, 4.9; N, 4.6%; M^+ 305.0722); $\bar{\nu}$max 1730 (C=O), 1690 (C=O), 1585, 1530 (C=S) cm^{-1}; δ_H and δ_C Tables 9 and 10.

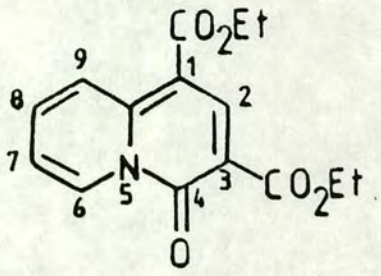
(ii) A yellow band yielded a yellow solid which was recrystallised from ethanol to give starting quinolizin-4-one derivative (0.150 g, 30%).

Table 9. ^{13}C n.m.r. spectral data for compounds (131), (133) and (142)[a]

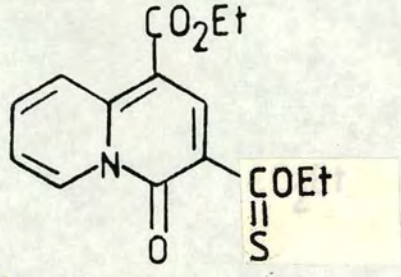
parent (131)		thioester (142)		thione (133)	
δ/ppm	ass.	δ	ass.	δ	ass.
14.1	sp^3CH_3	13.6	sp^2CH_3	13.8	sp^3CH_3
14.2	sp^3CH_3	14.1	sp^3CH_3	14.1	sp^3CH_3
60.7	sp^3CH_2	60.8	sp^3CH_2	61.4	sp^2CH_2
60.8	sp^3CH_2	68.3	sp^3CH_2	61.7	sp^2CH_2
101.5	sp^2C_1	101.8	sp^2C_1	109.2	sp^2C_1
105.4	sp^2C_3	115.5	sp^2C_3	119.2	sp^2CH
117.3	sp^2CH	117.3	sp^2CH	124.8	"
124.1	"	124.1	"	130.2	sp^2C_3
130.0	"	130.4	"	132.7	sp^2CH
136.4	"	136.2	"	134.7	"
144.0	"	144.0	"	135.0	"
146.8	sp^2C_{9A}	146.1	sp^2C_{9A}	144.8	sp^2C_{9A}
155.1	$sp^2C{=}O$ ring	154.2	$sp^2C{=}O$ ring	164.1	$sp^2C_1'{=}O$
164.4	$sp^2C{=}O$ ester	164.5	" ester	167.0	$sp^2C_3'{=}O$
165.0	$sp^2C{=}O$ ester	208.9	$sp^2C{=}S$	173.3	$sp^2C_4{=}S$

a) In $CDCl_3$ at 50.32 MHz

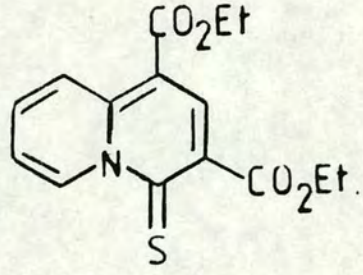
Table 10. ^{1}H n.m.r. spectra[a] of compounds (131), (133) and (142)



(131)[b]



(142)[b]



(133)[c]

Assign/δ_H[a]	(131)[b]	(142)[b]	(133)[c]
H-1	1.41 t 3H; 4.38 q 2H	1.43 t 3H; 4.40 q 2H	1.41 t 3H; 4.41 q 2H
H-2	9.14 s 1H	9.34 s 1H	8.36 s 1H
H-3	1.41 t 3H; 4.42 q 2H	1.55 t 3H; 4.79 q 2H	1.42 t 3H; 4.42 q 2H
H-6	9.51 "d"[d] 1H	9.54 "d"[d] 1H	10.75 d 1H
H-7	7.31 dt 1H	7.33 dt 1H	7.53 dt 1H
H-8	7.85 ddd 1H	7.85 ddd 1H	7.88 ddd 1H
H-9	9.35 "d"[d] 1H	9.37 "d"[d] 1H	9.46 d 1H
J/Hz	$J_{6,7}$ 7.1 Hz; $J_{6,8}$ 1.6; $J_{7,8}$ 6.9; $J_{7,9}$ 1.4; $J_{8,9}$ 9.1	$J_{6,7}$ 7.1 Hz; $J_{6,8}$ 1.6; $J_{7,8}$ 6.9; $J_{7,9}$ 1.5; $J_{8,9}$ 9.1	$J_{6,7}$ 7.0 Hz; $J_{6,8}$ 1.5; $J_{7,8}$ 7.1; $J_{7,9}$ 1.6; $J_{8,9}$ 9.1

a) In $CDCl_3$. b) At 80 MHz. c) At 200 MHz. d) Actually appears as a multiplet with doublet characteristics (d with fine splitting)

E4 Chemistry of a [3.3.3]cyclazine.

E4.2 Reactions of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with potential cycloaddition reagents.

E4.2.1 Reactions with stable dienophiles: cycloadditions and substitutions.

Reaction of the [3.3.3]cyclazine diester with diethyl acetylenedicarboxylate

a) In toluene

Under a dry nitrogen atmosphere, 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine (0.250 g, 0.80 mmol) and diethyl acetylenedicarboxylate (0.270 g, 1.60 mmol) were refluxed in dry toluene (20 ml) for 16 h. The solvent was removed under reduced pressure and the residual red oil was dissolved in dichloromethane and subjected to flash column chromatography on silica. Elution with various combinations of toluene, dichloromethane and diethyl ether removed two bands:

(i) a yellow band that yielded a purple-brown solid (0.017 g) which was identified as [3.3.3]cyclazine diester starting material, and

(ii) a dark red-brown band which gave a red solid. Recrystallisation of this solid from light petroleum (b.p. 60-80°C)-ethyl acetate gave tetraethyl 3a,6-dihydro-3a,6-ethenopyrido[2,1,6-de]quinolizine-1,3,4,5-tetracarboxylate (145) [0.242 g, 63%] as bright red prisms, m.p. 188-190°C (Found: C, 64.9; H, 5.6; N, 2.9. $C_{26}H_{27}NO_8$ requires C, 64.9; H, 5.6, N, 2.9%); $\bar{\nu}$max 1710 and

1660 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ Table 11; m/z 481 (M^+), 311 (100%).

b) In ethanol

Under a dry nitrogen atmosphere, 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine (0.100 g, 0.32 mmol) and diethyl acetylenedicarboxylate (0.060 g, 0.35 mmol) were refluxed together in ethanol (10 ml). After 5 h, t.l.c. showed the presence of at least two red spots (R_f< cyclazine) but cyclazine starting material still remained. Thus, a further quantity (0.060 g, 0.35 mmol) of the alkynediester was added and refluxing was continued for a further 17 h. The solvent was then removed in vacuo and the residual purple oil was subjected to preparative t.l.c. on silica in light petroleum (b.p. 60-80°C)-ethyl acetate (3:1). Several bands were removed from the plate and yielded products as detailed below in order of decreasing R_f value.

(i) From a brown band, a dark red-brown oil (0.010 g, 6%) was obtained. This material was sufficiently pure to be identified as 1,3-di(ethoxycarbonyl)-6-[1,2-di(ethoxycarbonyl)vinyl]pyrido[2,1,6-de]quinolizine (146), (Found: M^+ 481.1737. $C_{26}H_{27}NO_8$ requires M^+ 481.1736); $\delta_H(CDCl_3)$ Table 11; m/z 481 (M^+), 115 (100%).

(ii) A purple-brown band yielded a red oil (0.009 g) which was not characterised due to its lack of purity, but which was almost identical on t.l.c. to component (iii) below.

(iii) A brown band gave a purple-brown solid (0.010 g,

6%), which was sufficiently pure to be identified as 1,3-di(ethoxycarbonyl)-4-[1,2-di(ethoxycarbonyl)vinyl]-pyrido[2,1,6-de]quinolizine (147), (Found: $M^{+\cdot}$ 481.1732. $C_{26}H_{27}NO_8$ requires $M^{+\cdot}$ 481.1736); $\delta_H(CDCl_3)$ Table 11; m/Z 481 ($M^{+\cdot}$), 265 (100%).

(iv) A red band yielded a red oil (0.008 g, 4%) which was sufficiently pure to be identified as the cycloaddition-substitution product, 3a,6-dihydro-3a,6-etheno-7-[1,2-di(ethoxycarbonyl)vinyl]-1,3,4,5-tetra-(ethoxycarbonyl)pyrido[2,1,6-de]quinolizine (148), (Found: $M^{+\cdot}$ 651.2294. $C_{34}H_{37}NO_{12}$ requires $M^{+\cdot}$ 651.2316), $\delta_H(CDCl_3)$ Table 11; m/Z 651 ($M^{+\cdot}$), 481 (100%).

(v) From a red band on the plate was obtained a red solid, which was recrystallised from ether/n-pentane to give tetraethyl 3a,6-dihydro-3a,6-ethenopyrido-[2,1,6-de]quinolizine-1,3,4,5-tetracarboxylate (145) [0.024 g, 16%] as bright red prisms, m.p. 190°C, identical in all respects with the compound obtained when the reaction was carried out in toluene.

Attempted reactions of the [3.3.3]cyclazine diester with acyclic olefinic dienophiles

(a) With dimethyl fumarate

Under an inert atmosphere (N_2), 1,3-di(ethoxycarbonyl)-[3.3.3]cyclazine (0.150 g, 0.48 mmol) and dimethyl fumarate (0.139 g, 0.96 mmol) were refluxed together in dry toluene (15 ml) with t.l.c. monitoring (silica - CH_2Cl_2:Et_2O [4:1]). After 30 h, no reaction had occurred and the reaction mixture was cooled and loaded onto a flash column of silica.

Elution of the column with dichloromethane-ether (3:1) removed a yellow-green band which gave recovered cyclazine starting material (0.120 g, 80%) as purple-brown needles after recrystallisation from cyclohexane-THF. No cyclo-adduct was isolated.

(b) With dimethyl maleate

The experiment was carried out as described above for dimethyl fumarate. After 40 h, no change was apparent in the solution but a very faint orange-red spot was just visible on the t.l.c. plate at about half the Rf value of the cyclazine starting material. No work-up was performed on this reaction mixture.

(c) With fumaronitrile

1,3-Di(ethoxycarbonyl)[3.3.3]cyclazine (0.20 g, 0.64 mmol) and fumaronitrile (0.100 g, 1.30 mmol) were refluxed together in dry toluene (15 ml) under a dry nitrogen atmosphere. After 7.5 h, t.l.c. showed no product formation, and the cyclazine diester was recovered by flash column chromatography (silica) as purple-brown needles (0.170 g, 85%), m.p. 145-147°C after recrystallisation from cyclohexane-THF.

Reaction of the [3.3.3]cyclazine diester with cyclic olefinic dienophiles.

Reaction of the [3.3.3]cyclazine diester with N-phenyl-maleimide (PMI)

(a) In toluene

Under an inert atmosphere (N_2), 1,3-di(ethoxycarbonyl)-[3.3.3]cyclazine (0.200 g, 0.64 mmol) and N-phenylmaleimide

(0.224 g, 1.30 mmol) were refluxed together in dry toluene (15 ml). After 18 h refluxing with t.l.c. monitoring (silica-CH_2Cl_2:Et_2O [4:1]), a further amount (0.100 g) of PMI was added and refluxing was continued for a further 2 h. The reaction mixture was allowed to cool, the solvent was removed under reduced pressure, and the residue was subjected to flash chromatography on silica. Elution with dichloromethane-ether removed two bands as detailed below.

(i) A yellow-green band yielded recovered [3.3.3]-cyclazine diester (0.126 g, 63%), m.p. 145-148°C (from cyclohexane-THF).

(ii) A red band yielded a red solid which was recrystallised from ethyl acetate-chloroform to give N-phenyl-3a,4,5,6-tetrahydro-3a,6-etheno-1,3-di(ethoxycarbonyl)pyrido[2,1,6-de]quinolizine-4,5-dicarboximide (159), [0.062 g, 20%(54% based on unrecovered cyclazine starting material)], red needles, m.p. 197-200°C decomp. (Found: C, 69.3; H, 5.0; N, 5.7. $C_{28}H_{24}N_2O_6$ requires C,69.4; H, 5.0, N, 5.8%), $\bar{\nu}$max 1780, 1715, 1650 (C=O) cm^{-1}, λmax (EtOH) 218, 266 sh, 272, 307, 374, 495 sh, 515 and 552 sh nm ($\log_{10}\varepsilon$ 4.09, 3.98, 4.02, 4.18, 3.82, 3.72, 3.78 and 3.58), δ_H Table 12; m/z 484 ($M^{+\cdot}$), 311 (100%).

A small amount of this cycloadduct was refluxed in toluene and the reaction was monitored by t.l.c. [silica/CH_2Cl_2-Et_2O (4:1)], which showed that the cycloadduct reverted to starting materials. On allowing the system to cool, the red spot corresponding to the cycloadduct reappeared.

(b) In benzene

Repetition of the above experiment using 1,3-di-(ethoxycarbonyl)[3.3.3]cyclazine (0.200 g, 0.64 mmol) and N-phenylmaleimide (0.244 g, 1.30 mmol) in dry benzene (15 ml) with refluxing for 16 h and slow cooling for 6 h gave, after flash column chromatography (silica):

(i) a trace amount of recovered starting cyclazine, and

(ii) the PMI-cycloadduct (0.144 g, 46%) identical with the product obtained in toluene.

Reaction of the [3.3.3]cyclazine diester with maleic anhydride

1,3-Di(ethoxycarbonyl)[3.3.3]cyclazine (0.150 g, 0.48 mmol) and maleic anhydride (0.095 g, 0.96 mmol) were refluxed together in dry toluene (12 ml) under a nitrogen atmosphere with t.l.c. monitoring [silica/CH_2Cl_2:Et_2O (4:1)]. Little reaction occurred and, after 7 h, refluxing was ceased and the reaction mixture was allowed to cool slowly. The toluene solution was decanted off to leave a red solid (0.100 g, 51%), the ^1H n.m.r. spectrum of which showed it to be a slightly impure sample of 3a,4,5,6-tetrahydro-3a,6-etheno-1,3-di(ethoxycarbonyl)-pyrido[2,1,6-de]quinolizine-4,5-dicarboxylic anhydride (160), $\bar{\nu}$max 1790, 1740, 1640 (C=O) cm^{-1}, $\delta_H(CDCl_3)$ Table 13; m/z 311 (M^{+} - maleic anhydride), (Found: M^{+} 311.1158. $C_{18}H_{17}NO_4$ requires 311.1157).

Attempted purification by column chromatography or by recrystallisation caused extensive decomposition.

Reaction of the [3.3.3]cyclazine diester with 1,4-benzoquinone

Under a dry nitrogen atmosphere, 1,3-di(ethoxycarbonyl)-[3.3.3]cyclazine (0.200 g, 0.64 mmol) and 1,4-benzoquinone (0.083 g, 0.77 mmol) were stirred together at room temperature in dry toluene (15 ml). T.l.c. showed that no reaction was occurring at room temperature and thus the mixture was refluxed. After 1.5 h, no reaction having occurred, a further amount (0.055 g) of benzoquinone was added and refluxing was continued. After 30 h, t.l.c. revealed the formation of oxidation products recognisable by their Rf values in comparison with authentic samples (section 4.3). More benzoquinone (0.100 g) was then added and the reaction mixture was refluxed for a further 22 h. At this point t.l.c. revealed that decomposition was occurring and that the oxidation products [which included the [2.3.3]cyclazines (181) and (183), and the 6,6'-bicyclazinyl compound (74)] were still present in no more than trace amounts.

Reaction of the 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with dialkyl azodicarboxylates

(a) With diethyl azodicarboxylate ($EtO_2C-N=N-CO_2Et$)

1,3-Di(ethoxycarbonyl)[3.3.3]cyclazine (0.250 g, 0.80 mmol) was dissolved in dry THF (10 ml) under a dry nitrogen atmosphere. To the stirred solution was added a solution of diethyl azodicarboxylate (0.154 g, 0.88 mmol) in THF (5 ml) dropwise at room temperature. The clear yellow solution was stirred at room temperature with t.l.c. monitoring [silica/CH_2Cl_2-Et_2O (4:1)]. After 5 min. multiple

product formation was noted (⩾ 6 components), but since the t.l.c. showed no sign of decomposition, stirring was continued for 2.5 h, after which time the solvent was removed in vacuo. The residue was redissolved in dichloromethane and deposited on to anhydrous sodium sulphate by re-evaporation. The resulting dry powder was then packed on to the top of a column of t.l.c. silica [Kieselgel 60H (without binding)] (140 x 25 mm) and solvent mixtures of toluene-dichloromethane-ether were sucked through the column (c.f. dry flash column chromatography)[90] giving an initial separation of bands on the silica. Continued elution was then carried out by supplying the solvent under pressure (i.e. as for normal m.p.l.c.). The fractions so obtained were further processed by dry flash column chromatography (on silica in dichloromethane containing increasing quantities of ether) or by preparative t.l.c. [silica/CH_2Cl_2-Et_2O (5:1)]. The products obtained by this combination of chromatographic procedures are detailed below in order of decreasing chromatographic mobility.

(i) Part of the cyclazine diester (0.050 g) was recovered.

(ii) A purple-brown oil was triturated with ether-pentane to give a brownish-green solid (0.125 g). Recrystallisation from diethyl ether by cooling the solution below room temperature yielded (25%) 1,3-di(ethoxycarbonyl)-4-[1,2-di(ethoxycarbonyl)hydrazino]-pyrido-[2,1,6-de]quinolizine (164a), brownish-green prisms

(from cyclohexane), m.p. 120-126°C. decomp., darkening at 108°C, (Found: M^+ 485.1795. $C_{24}H_{27}N_3O_8$ requires M^+ 485.1798); $\bar{\nu}$max 3480 (NH), 1745, 1720, 1685 and 1660 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ Table 14. Despite several attempts, satisfactory analytical data could not be obtained for this compound. The results could, however, be accommodated on the assumption that the sample contained residual cyclohexane (crystallisation solvent) which had not been removed during vacuum drying.

(iii) A brown oil (0.080 g) obtained from an orange-yellow band contained at least four components. Preparative t.l.c. [silica/CH_2Cl_2-Et_2O (5:1)] was ineffective in fully separating these products which therefore remain uncharacterised.

(iv) A brownish-green solid (0.076 g) obtained by trituration of a purple-brown oil was recrystallised from cyclohexane-THF to give 1,3-di(ethoxycarbonyl)-6,7-bis-(1,2-di(ethoxycarbonyl)hydrazino]pyrido[2,1,6-de]quinolizine (164c), as greenish-brown prisms (0.035 g, 7%), m.p. 114°C decomp., (Found: C, 54.9; H, 5.8; N, 10.3, M^+ 659.2439. $C_{30}H_{37}N_5O_{12}$ requires C, 54.6; H, 5.6; N, 10.6%; M^+ 659.2438; $\bar{\nu}$max 3390br (NH), 1735br, 1670 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ [200 MHz] 7.8 (br.s, 2H), 7.2-7.3 (m), 6.7-6.9 (m, 2H), 5.7-5.8 (m, 2H), 4.0-4.5 (m, 18H), 1.2-1.4 (m, 18H); δ_H (d^6-dmso) Table 14.

(v) A brown solid (0.040 g) obtained from a yellow-green band could not be obtained pure and remains uncharacterised.

(vi) A brown oil (0.010 g) obtained from an orange band was a mixture of at least two components.

(b) With di-t-butyl azodicarboxylate ($Bu^tO_2C-N=N-CO_2Bu^t$)

Using the same procedure as in (a) above, 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine (0.250 g, 0.80 mmol) was treated with di-t-butyl azodicarboxylate (0.203 g, 0.88 mmol) in THF (5 ml). After 1 h, a further amount (0.200 g, 0.88 mmol) of the azo- reagent was added and stirring was continued for a further 4.5 h. The solvent was then removed in vacuo to leave a purple-brown oil which was shown by t.l.c. to be a multicomponent mixture. A partial separation was carried out by m.p.l.c. on a column (160 x 25 mm) of t.l.c. alumina (Fluka type G, 6% deactivated, neutral) eluting with various combinations of light petroleum (b.p. 40-60°C), dichloromethane and diethyl ether, to give the following fractions.

(i) Part of the cyclazine diester (0.072 g) was recovered.

(ii) A brown-green solid (0.107 g) obtained from a yellow band was shown by t.l.c. to be a mixture of at least two components. Further separation by flash column chromatography on silica in dichloromethane-ether gave (a) a small amount of an uncharaterised orange crystalline solid (0.004 g), (b) a yellow-brown oil (0.057 g) which was crystallised from cold diethyl ether to give 1,3-di(ethoxycarbonyl)-4-[1,2-di(t-butoxycarbonyl)-hydrazino]pyrido[2,1,6-de]quinolizine (164b) (0.026 g,6%) as small greenish-brown crystals, m.p. 172-174°C decomp.,

(Found: $M^{+\cdot}$ 541.2429. $C_{28}H_{35}N_3O_8$ requires $M^{+\cdot}$ 541.2424; $\bar{\nu}$max 3380 (NH), 1740, 1715, 1765 (C=O) cm^{-1}, $\delta_H(CDCl_3)$ [80 MHz) 7.15 (s, 1H), 6.9-7.2 (m, 1H), 6.2-6.7 (m, 2H), 5.3-5.6 (m, 2H), 3.9-4.2 (q, 4H), 1.4-1.6 (m x s, 18H), 1.1-1.3 (m x t, 6H), m/z 541 ($M^{+\cdot}$), 325 (100%), and (c) an incompletely characterised brown solid (0.002 g), m/z 541.

(iii) A brown oil (0.060 g) obtained from a yellow-green band was further separated by preparative t.l.c. [silica/CH_2Cl_2-Et_2O (7:1)] to give (a) a pale green solid (0.003 g), $\bar{\nu}$max 3300 (NH), 1745, 1690, 1670 (C=O) cm^{-1}; m/z 541 ($M^{+\cdot}$), 326 (100%) and (b) a pale brown solid (0.016 g) identified as compound (165)[§], m.p. 170°C decomp.; (Found: $M^{+\cdot}$ 495.1980. $C_{26}H_{29}N_3O_7$ requires 495.2005); $\bar{\nu}$max 1760, 1725 (C=O), 1690 (CON), 1655 cm^{-1}, $\delta_H(CDCl_3)$ [80 MHz] 7.32 (s, 1H, H-2), 7.02 (dd, 1H, H-11), 6.57 (d, 1H, H-7), 6.37 (t, 1H, H-10), 5.66 (dd, 1H, H-9), 5.46 (d, 1H, H-8), 4.04 (q, 2H, $\underline{CH_2}CH_3$), 1.50/1.46 (2 x s, 18H, $C(Me)_3$), 1.20 (t, 3H, $CH_2\underline{CH_3}$), ($J_{7,8}$ 8.7; $J_{9,10}$ 8.3; $J_{10,11}$ 8.2; $J_{9,11}$ 1.4 Hz); m/z 495 ($M^{+\cdot}$), 351(100%).

(iv) A brown oil (0.240 g) obtained from a yellow tailing band was shown by t.l.c. to be a multicomponent mixture. Preparative t.l.c. failed to give any of these components in a pure state.

---

§ 3,4-di(tert-butyl)-7-ethyl 3,4,5,10b-tetrahydro-5H-5--oxo-3,4,10b-triazapyrene-3,4,7-tricarboxylate

E4.2.2 Attempted reactions of 1,3-di(ethoxycarbonyl)-[3.3.3]cyclazine with benzyne

1-(2-Carboxyphenyl)-3,3-dimethyltriazene

The title compound was prepared by the method of Elks and Hey[91] by diazotisation[86] of anthranilic acid (10.00 g, 0.07 mol) and the reaction of the diazonium salt with aqueous dimethylamine. The triazene (9.13 g, 65%) was obtained as long colourless needles from ethanol, m.p. 122-125°C decomp. (lit.[90] m.p. 122-124°C decomp.).

(a) Thermal decomposition of 1-(2-carboxyphenyl)-3,3-dimethyltriazine in the presence of the cyclazine diester

1,3-Di(ethoxycarbonyl)[3.3.3]cyclazine (0.200 g, 0.64 mmol) and the triazine reagent (0.070 g, 0.33 mmol) were stirred and refluxed together in chlorobenzene (10 ml) under a dry N_2 atmosphere. The reaction was monitored by t.l.c. [silica/CH_2Cl_2-Et_2O (4:1)] and, after 8 h, a further amount (0.070 g) of triazene reagent was added and refluxing continued. After 15 h, t.l.c. revealed multiple product formation but since an appreciable amount of cyclazine starting material remained, a further amount (0.070 g) of triazene was added, and refluxing was continued for a further 9 h. The t.l.c. then showed multiple product formation including numerous yellow, orange and pink spots on the t.l.c. plate, and thus the solution was cooled to room temperature and the solvent was removed under reduced pressure to give a purple-brown oil. Attempts to obtain some of the components

by preparative t.l.c. (silica/5% ethanol in ethyl acetate) gave only trace amounts of red solids and brown oils including the cyclazine diester starting materisl (~50% recovered crude). The red solids decomposed rapidly even when stored in the cold; their low Rf values on t.l.c. were not consistent with either a benzyne cycloadduct or a benzo[3.3.3]cyclazine structure.

(b) Thermal decomposition of 2-phenyliodoniobenzoate in the presence of the cyclazine diester

Under a nitrogen atmosphere, 2-phenyliodoniobenzoate[61] (0.208 g, 0.64 mmol) was added in small aliquots to a refluxing solution of 1,3-di(ethoxycarbonyl)[3.3.3]-cyclazine (0.200 g, 0.64 mmol) in γ-butyrolactone (4 ml). Heating was stopped after a total of 0.75 h, when t.l.c. monitoring [silica/CH_2Cl_2-Et_2O (4:1)] showed extensive decomposition (dark material on base-line). The solvent was removed in vacuo and the brown oily residue checked once again by t.l.c. which revealed a complex mixture containing more than seven minor components in addition to decomposition product. No attempt was made to isolate these minor products.

E4.2.3 Reaction of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with ethoxycarbonylcarbene

The procedure used in this experiment was based on that of Doyle et al[64] for rhodium (II)-catalysed generation of ethoxycarbonylcarbene in the presence of various alkenes.

Under a dry N_2 atmosphere, 1,3-di(ethoxycarbonyl)-

[3.3.3]cyclazine (0.500 g, 1.6 mmol) and rhodium(II) acetate (0.005 g) were stirred together in the minimum amount of dry dichloromethane (~10 ml). The solution was brought to reflux and, over a period of 15 h, a solution of ethyl diazoacetate (0.250 g, 2.2 mmol) in dichloromethane (5 ml) was added from a motor-driven syringe, keeping the tip of the syringe needle below the surface of the solution. After the 15 h had elapsed, t.l.c. [silica/toluene] revealed a multicomponent product mixture, but cyclazine starting material was still present. Accordingly a further amount of ethyl diazoacetate (0.13 g) in dichloromethane (2.5 ml) was added over a further 7 h period. The solution was then refluxed for a further 0.5 h and the solvent was removed under reduced pressure. T.l.c. of the residue showed that some decomposition had occurred and that a number of products of similar Rf had been formed. The decomposition product (strongly adsorbed) was removed by passing the mixture through a flash column of alumina (neutral, 10% deact.), in CH_2Cl_2-Et_2O, and the removed material was subjected to preparative t.l.c. [silica/15% Et_2O in PhMe]. This yielded the following isolable materials.

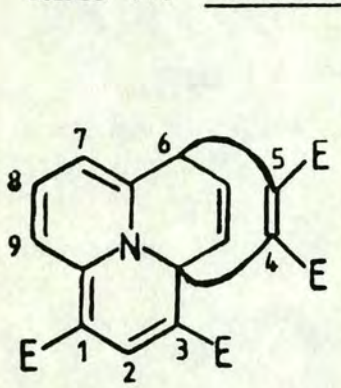
(i) From the alumina flash column was recovered an impure sample of the [3.3.3]cyclazine diester starting material. This material was evident by t.l.c. only and was not recovered pure.

(ii) A yellow-brown band gave a small amount (0.024 g) of an orange solid which was recrystallised from light

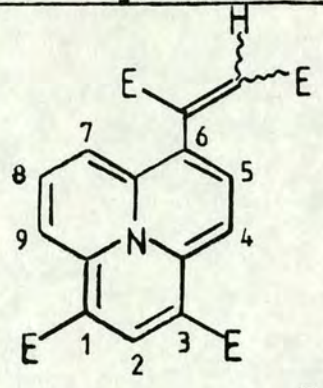
petroleum (b.p. 60-80°C)-ethyl acetate to give an orange solid identified (see text, section 4.2.3) as a mixture of 6-(ethoxycarbonylmethyl)-1,3-di(ethoxycarbonyl)pyrido-[2,1,6-de]quinolizine (178) and 6,7-di(ethoxycarbonyl-methyl)-1,3-di(ethoxycarbonyl)pyrido[2,1,6-de]quinolizine (179), m.p. 155-160°c, (Found: $M^{+\cdot}$ 397.1525. $C_{22}H_{23}NO_6$ requires $M^{+\cdot}$ 397.1525; Found: $M^{+\cdot}$ 483.1893. $C_{26}H_{29}NO_8$ requires $M^{+\cdot}$ 483.1893); $\bar{\nu}$max 1730, 1655 (C=O) cm^{-1}; λmax (EtOH) [qualitative only] 203, 248, 286, 314i, 329, 398, 436sh and 460 n.m.; δ_H Table 15.

(iii) A pink-red band yielded a small amount (0.008 g) of a red solid tentatively identified as a slightly impure sample of tetraethyl cyclopenta[ij]pyrido[2,1,6-de]-quinolizine-1,2,5,7-tetracarboxylate (180); m.p. ~180°C; (Found: $M^{+\cdot}$ 479.1580. $C_{26}H_{25}NO_8$ requires $M^{+\cdot}$ 479.1580); λmax (EtOH) [qualitative only] 205, 222, 248, 266, 284, 340, 356, 380, 398, 438, 462, 510 and 584sh nm; $\delta_H(CDCl_3)$ [200 MHz] 8.89 (s, 1H, H-2), 8.70 (d, 2H, H-4/9), 8.57 (d, 2H, H-5/8), 4.49 (q, 4H, CH_2 [ester]), 4.48 (q, 4H, CH_2 [ester]), 1.47 (t, 6H, CH_3 [ester]); 1.46 (t, 6H, CH_3 [ester]), ($J_{4,5}$ 9.2 Hz).

Table 11. ^{1}H n.m.r. spectra of cycloadducts and substitution products (145-148)

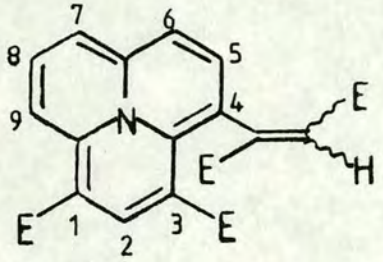


(145)

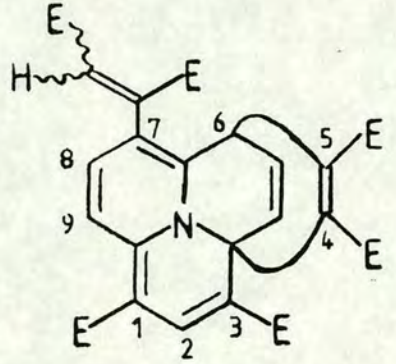


(146)

E = CO_2Et.



(147)

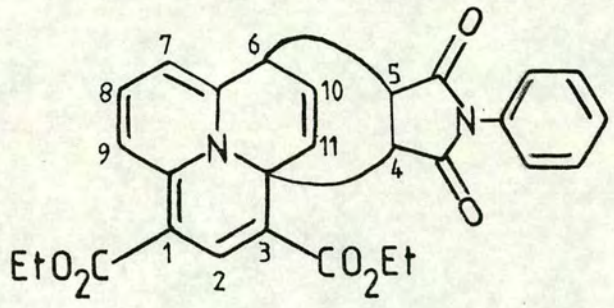


(148)

	δ/H[a]	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	Other protons	Coupling constants J/Hz
(145)	b)	[4.2,q] [1.3,t]	8.21 (s)	[4.2,q] [1.3,t] ⟷	[4.2,q] [1.3,t]	[4.2,q] [1.3,t]	4.99 (dd)	6.42 (dd)	7.06 (dd)	8.43 (dd)	6.78 (dd) 6.86 (dd)	$J_{7,8}$ 6,7; $J_{8,9}$ 9.2; $J_{7,9}$ 1.4 $J_{etheno-etheno'}$ 6.9 $J_{6,etheno}$ 5.9; $J_{6,etheno'}$ 2.1 Hz
(146)	c)	[4.0-4.2,q] [1.2-1.4,t]	7.20 (s)	[4.0-4.2,q] [1.2-1.4,t]	6.76 (d)	5.93 (d)	[4.0-4.2,q] [1.2-1.4,t]	4.92 (dd)	6.13 (t)	6.80 (dd)	H-6'C=CHE 6.79 (s)	$J_{7,8}$ 8.2; $J_{8,9}$ 8.3; $J_{7,9}$ 1.5; $J_{4,5}$ 8.5 Hz
(147)	c)	[3.8-4.5,q] [1.0-1.4,t]	7.26 (s)	[3.8-4.5,q] [1.0-1.4,t] ⟷		6.31 (d)	5.62 (d)	5.64 (dd)	6.48 (t)	7.13 (dd)	H-4'C=CHE 6.46 (s)	$J_{7,8}$ 8.2; $J_{8,9}$ 8.3; $J_{7,9}$ 1.6; $J_{5,6}$ 8.8 Hz
(148)	c)	[4.0-4.4,q] [1.2-1.3,t]	8.21 (s)	[4.0-4.4,q] [1.2-1.3,t] ⟷			4.93 (dd)	[4.0-4.4,q] [1.2-1.3,t]	6.81 (d)	8.45 (d)	etheno 6.7-6.8 H-7'C=CHE 7.13 (s)	$J_{8,9}$ 9.4; $J_{6,etheno}$ 5.1,2.9 Hz

a) Values in parenthesis refer to substituents. b) 200 MHz ($CDCl_3$) c) 80 MHz ($CDCl_3$)

Table 12. 360 MHz ^{1}H n.m.r. of the cycloadduct of (47a) with N-phenylmaleimide.



(159)

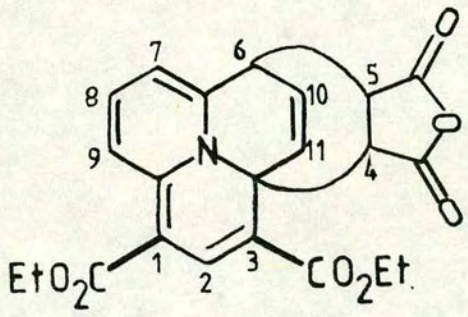
δ($CDCl_3$)	m	No. of protons	Decoupling expts.[a]					Assignment
8.55	dd	1H		+				H-9
8.16	s	1H						H-2
7.30-7.40	m	3H						aromatic
7.10	dd	1H		+				H-8
6.88-6.92	m	2H						aromatic (ortho to N)
6.74	dd	1H			+	hν		H-11
6.64	dd	1H			hν	+		H-10
6.30	dd	1H		hν				H-7
4.24	q	2H						CH_2 (1-CO_2Et)
4.17	dq	1H						CH_2 (3-CO_2Et)
4.12	dq	1H						
4.10	ddd	1H	+		+	+		H-6
4.08	d	1H	+					H-4
3.43	dd	1H	hν					H-5
1.34	t	3H						CH_3(CO_2Et)
1.29	t	3H						

Coupling constants:-

$J_{8,9}$ 9.4; $J_{7,8}$ 6.7; $J_{7,9}$ 1.4; $J_{10,11}$ 7.6; $J_{6,10}$ 6.3; $J_{6,11}$ 1.7; $J_{5,6}$ 3.3; $J_{4,5}$ 9.1; $J_{gem(ester)}$ 10.7; $J_{vic(ester)}$ 7.1 Hz

a) Decoupling experiments: hν indicates irradiation frequency; + indicates definite effect

Table 13. 200 MHz ^1H n.m.r. of the cycloadduct of (47a) with maleic anhydride.



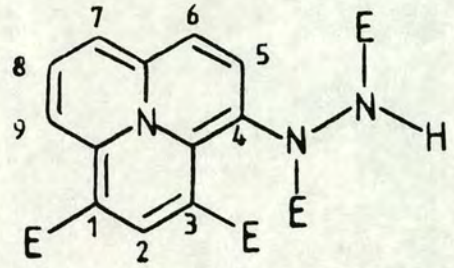
(160)

δ($CDCl_3$)	m	No. of protons	Assignment
8.52	dd	1H	H-9
8.18	s	1H	H-2
7.13	dd	1H	H-8
6.69	dd	1H	H-11
6.61	dd	1H	H-10
6.33	dd	1H	H-7
4.26	d	1H	H-4
3.9-4.2	mq	4H	2 x CH_2 (ester)
4.0	m	1H	H-6
3.62	dd	1H	H-5
1.34	t	3H	CH_3 (ester)
1.30	t	3H	

Coupling constants:-

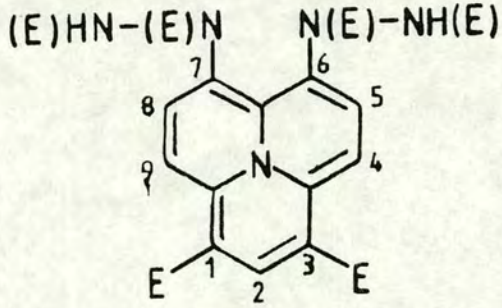
$J_{8,9}$ 7.4; $J_{7,8}$ 6.8; $J_{7,9}$ 1.4; $J_{10,11}$ 7.7; $J_{6,10}$ 6.0; $J_{6,11}$ 1.8; $J_{5,6}$ 3.4; $J_{4,5}$ 9.8; J_{vic} 7.1 Hz

Table 14. [200 MHz] ^{1}H n.m.r. spectra of compounds (164a) and (164c) in d^6-dmso



(164a)

E = CO_2Et.

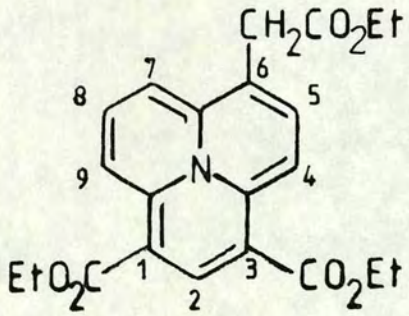


(164c)

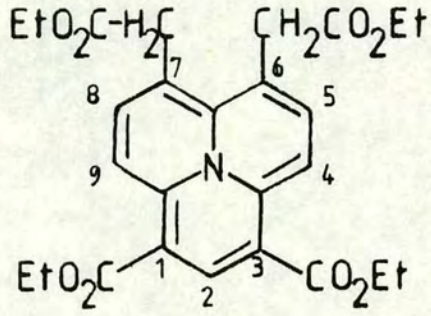
δ_H (d^6-dmso)[a]	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	Coupling constants
(164a)[b]	1.1-1.3 (t) 3.9-4.2 (q)	7.02 (s)	1.1-1.3 (t) 3.9-4.2 (q) (7.90 br.s[d])		6.48 (d)	5.88 (d)	5.86 (dd)	6.65 (t)	6.91 (dd)	$J_{5,6}$ 9.2 Hz $J_{7,8}$ 8.1 $J_{8,9}$ 8.3 $J_{7,9}$ 1.5
(164c)[c]	1.17 (t) 4.04 (q)	7.33 (s)	1.17 (t) 4.04 (q)	6.90 (d)	6.25 (d)	1.22 (t) 4.13 (q) 8.08[d] (br s)		6.25 (d)	6.90 (d)	$J_{4,5}$ 9.0 Hz

a) Values in parenthesis are for substituent groups
b) Spectrum run at 373 K. Resolution decreases at lower temps.
c) Spectrum run at 381 K. Resolution decreases at lower temps.
d) Peak removed on shaking the sample with D_2O, [NH].

Table 15. 200 MHz ^{1}H n.m.r. data for the substitution products (178) and (179)



(178)



(179)

$\delta_H(CDCl_3)$[a] /H	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	Coupling constants J/Hz
(178)	4.0-4.2 (q) 1.2-1.3 (t)	7.17 (s)	4.0-4.2 (q) 1.2-1.3 (t)	6.70 (d)	6.10 (d)	2.72 (s/CH_2) 4.0-4.2 (q) 1.2-1.3 (t)	5.22 (dd)	6.23 (t)	6.84 (dd)	$J_{4,5}$ 8.4; $J_{7,8}$ 8.4; $J_{8,9}$ 8.4; $J_{7,9}$ 1.4 Hz J_{vic} 7.1 Hz
(179)	4.0-4.2 (q) 1.2-1.3 (t)	7.29 (s)	4.0-4.2 (q) 1.2-1.3 (t)	6.90 (d)	6.22 (d)	3.03 (s/2 x CH_2) 4.0-4.2 (q) 1.2-1.3 (t)		6.22 (d)	6.90 (d)	$J_{4,5}$ 8.6 Hz J_{vic} 7.1 Hz

a) Values in parenthesis indicate the resonance value of the substituent group

E4.3 Oxidation reactions of a [3.3.3]cyclazine derivative

E4.3.1 Oxidation of a [3.3.3]cyclazine derivative - Formation of cyclazinones

Oxidation of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine on a t.l.c. plate

The cyclazine diester (0.050 g, 0.2 mmol) was loaded onto a preparative t.l.c. plate as a dichloromethane solution. The plate was then developed in light petroleum (b.p. 40-60°C)-CH_2Cl_2 (1:1) and left exposed to light and air at room temperature. After eleven days, the plate was redeveloped in ethyl acetate and the broad yellow bands that resulted were removed from the plate as one. Extraction of the adsorbent with ethyl acetate and evaporation of the extract gave a yellow-brown solid (0.030 g) which was rechromatographed on a new preparative t.l.c. plate (silica/EtOAc) to give the following fractions, listed in order of decreasing Rf.

(i) A fluorescent yellow band yielded an orange solid (Y1) which was recrystallised from light petroleum (b.p. 60-80°C)-ethyl acetate to give orange needles (0.005 g, 10%), m.p. 106-109°C, m/z 313 ($M^{\cdot+}$), 240 (100%). [This product, as obtained in later experiments, proved to be diethyl 5-oxo-5H-pyrrolo[2,1,5-de]quinolizine -1,2--dicarboxylate (181)].

(ii) A yellow band yielded an orange-yellow solid (Y2) which was recrystallised from cyclohexane-ethyl acetate to give yellow needles (0.003 g, 6%), m.p. 186-188°C, m/z 313 ($M^{\cdot+}$). [This product as obtained in later

experiments, proved to be diethyl 3-oxo-3H-pyrrolo-[2,1,5-de]quinolizine-1,2-dicarboxylate (183)].

(iii) Pink and red bands of lower chromatographic mobility were too faint to allow isolation of the products (R1 and R2).

Similar experiments carried out on both silica and alumina t.l.c. plates, in the presence of and in the absence of light, gave similar results.

Identification of the yellow oxidation products (Y1 and Y2)

The cyclazine diester (0.100 g, 0.4 mmol) dissolved in THF (10 ml) was stirred at room temperature with t.l.c. silica (0.100 g). After 1 h, no apparent reaction had occurred and thus a further amount (0.900 g) of silica was added and the stirred mixture was then refluxed with t.l.c. monitoring. After 5 h, trace amounts of the yellow and pink materials observed previously were evident by t.l.c., and thus refluxing was continued, until after 8 days, only a trace of cyclazine diester remained (by t.l.c.). The mixture was then cooled and filtered and the filtrate was evaporated leaving a dark brown oil, which was then subjected to flash column chromatography (silica). Elution with ratios of light petroleum (b.p. 40-60°C)-CH_2Cl_2-Et_2O-EtOAc gave the following fractions.

(i) A purple-brown solid (0.020 g) isolated from a yellow band on the column. This material was identified as recovered [3.3.3]cyclazine diester.

(ii) A purple-blue band on the column that yielded a small amount (0.001 g) of a dark blue solid. This

material was not characterised.

(iii) A fluorescent yellow-green band on the column that gave a small amount of an orange solid (Y1). Vacuum sublimation (110°C/0.05 mmHg) and recrystallisation (cyclohexane-ethyl acetate) gave a small amount (0.004 g) of diethyl 5-oxo-5H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (181) as yellow needles, $\bar{\nu}$max 1710, 1605 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ [200 MHz] 8.85 (dd, 1H, H-8), 8.58 (dd, 1H, H-6), 8.27 (d, 1H, H-3), 7.94 (t, 1H, H-7), 7.13 (d, 1H, H-4), 4.53 (q, 2H, CH_2), 4.47 (q, 2H, CH_2), 1.46 (t, 3H, CH_3), 1.44 (t, 3H, CH_3), ($J_{3,4}$ 10.1; $J_{6,7}$ 7.6; $J_{7,8}$ 8.6; $J_{6,8}$ 1.1 Hz); m/z 313 ($M^{+\cdot}$). This characterisation was proven by comparison with the product of unambiguous synthesis (section E6.2).

(iv) A yellow band on the column that yielded an orange solid (Y2). Vacuum sublimation (110°C/0.05 mmHg) and recrystallisation (cyclohexane-ethyl acetate) gave diethyl 3-oxo-3H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (183) as orange-yellow needles (0.006 g), m.p. 186-189°C; $\bar{\nu}$max 1740/1710, 1610 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ [200 MHz] 8.79 (dd, 1H, H-8), 7.93 (d, 1H, H-5), 7.82 (d, 1H, H-7), 7.81 (d, 1H, H-6), 7.32 (d, 1H, H-4), 4.59 (q, 2H, CH_2), 4.45 (q, 2H, CH_2), 1.48 (t, 3H, CH_3), 1.43 (t, 3H, CH_3), ($J_{4,5}$ 9.9, $J_{6,7}$ 3.2, $J_{7,8}$ 6.5 Hz); m/z 313 ($M^{+\cdot}$). This material was identical to that synthesised by the unambiguous route described in section E6.2.

Attempt to react the [3.3.3]cyclazine derivative with chemically generated singlet oxygen

Triphenyl phosphite ozonide

A solution of triphenyl phosphite ozonide [$(PhO)_3PO_3$] was prepared according to the method of Bartlett et al[66].

Dry ozone was passed through dry dichloromethane (10 ml) at -78°C, contained in a 3-necked 50 ml round-bottomed flask equipped with a magnetic stirrer and a dropping funnel, until a clear blue colour arose. The resulting blue solution was then stirred at -78°C whilst triphenyl phosphite (0.232 g, 0.74 mmol) in dichloromethane (2 ml) was added dropwise during 0.5 h. The persistence of the blue colour signified the presence of an excess of ozone which was then removed by purging with nitrogen for 0.5 h.

Reaction with the cyclazine diester

The ozonide solution was held at -78°C and stirred under nitrogen whilst 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine (0.115 g, 0.37 mmol) in dichloromethane (10 ml) was added dropwise. A chilled mixture (1:1) of methanol and pyridine (10 ml) was then added and the solution was stirred at -78°C for 1 h, and allowed to come slowly to room temperature. The solvent was evaporated and the dark residue was subjected to preparative t.l.c. [silica/CH_2Cl_2-Et_2O (4:1)] with the following results.

(i) A green band yielded an unidentified green-brown oil (0.001 g).

(ii) A fluorescent yellow band yielded 1,2-di(ethoxy-

carbonyl)[2.3.3]cyclazin-5-one (0.001 g) as an orange-yellow solid.

(iii) A yellow band yielded 1,2-di(ethoxycarbonyl)-[2.3.3]cyclazin-3-one as an orange-yellow solid.

(iv) A red band yielded a red oil (0.001 g), m/z 341 ($M^{+\cdot}$), which was not sufficiently pure for identification by other spectroscopic techniques.

Several other weaker coloured bands (orange and reds) noted on the preparative t.l.c. plate were not collected.

Action of oxidants on 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine

The cyclazine (0.1-0.3 g) was treated with various oxidants under the conditions outlined in Table 17, (discussion section 4.3.1) which also lists the products obtained. The reactions were monitored by t.l.c. and, if consumption of cyclazine appeared to slow down or stop, more reagent was added. The reactions were stopped when little or no cyclazine remained or when the formation of decomposition products (dark base-line spot on t.l.c.) was judged to be occurring.

The reaction conditions, and the methods of work-up and chromatography, are specified in more detail in Table 27.

Oxidation of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with t-butyl hydroperoxide in the presence of iron(III)chloride

1,3-Di(ethoxycarbonyl)[3.3.3]cyclazine (0.200 g, 0.64 mmol) and t-butyl hydroperoxide (0.300 g, 3.33 mmol) were dissolved in dry acetonitrile (40 ml) and ferric chloride (0.025 g) dissolved in the minimum volume of

Table 27.

Reagent	mol. equiv.[a]	solvent	Reaction time [b]	work-up	chromatography
Ag_2O	2.4	dry THF	7	A	D
Bu_4NIO_4[d]	1.1 + 0.23	CH_2Cl_2	6 + 17	A	D
Bu_4NIO_4	1.1 + 2.2	THF-H_2O(15:1)	32 + 16	A	D
$(C_5H_5NH)_2Cr_2O_7$[e]	1.1 + 0.42	CH_2Cl_2	7 + 17	A	D
NaOCl	6.2 + 9.3	CH_2Cl_2-H_2O	7 + 48	B, A	E
CrO_3	2.1	AcOH	120	C, B, A	F
H_2O_2-$MnCl_2$[c]	1.0	THF-H_2O	27 + 6	B, A	F
H_2O_2-$FeCl_3$[c]	excess	MeCN-H_2O	0.05	None	Analytical t.l.c. only

a) moles reagent/moles cyclazine

b) hours with initial reagent + hours after addition of further reagent

c) catalyst

d) ref. 67

e) ref. 68

A. evaporation of solvent

B. extraction into CH_2Cl_2

C. neutralisation with Na_2CO_3

D. column chromatography on neutral, deactivated alumina, eluting with various combinations of light petroleum (b.p. 40-60°C), PhMe, CH_2Cl_2 and EtOAc.

E. column chromatography on silica (eluting with CH_2Cl_2-EtOAc).

F. preparative t.l.c. on silica in EtOAc, CH_2Cl_2-EtOAc or CH_2Cl_2-Et_2O

acetonitrile was added, with stirring, at room temperature. The solution was heated under reflux at 80°C, whereupon the yellow-green cyclazine colour gave way to a deep red after a few minutes. Refluxing was continued for 1 h, and the mixture was cooled and the solvent evaporated. The residual red oil, which showed at least 8 components on t.l.c. (silica-ethyl acetate), was subjected to dry flash column chromatography on t.l.c. silica (Kieselgel GF254). Several bands were collected by elution with a solvent gradient (5% incremental) of ethyl acetate in light petroleum (b.p. 40-60°C) [Note 1]. These are described below in order of decreasing Rf value.

(i) A fluorescent yellow-green band gave the 1,2-di(ethoxycarbonyl)[2.3.3]cyclazin-5-one (0.025 g, 12%).

(ii) A red band that yielded an oil which, upon trituration with ether-pentane, became a red solid (0.014 g, R2A, 5%). This product was identified as 6-t-butoxy-1,3-di(ethoxycarbonyl)-4-oxo-4H-pyrido[2,1,6-de]-quinolizinium-9-olate, (190), m.p. 138-141°C; (Found: $M^{+\cdot}$ 413.1474. $C_{22}H_{23}NO_7$ requires $M^{+\cdot}$ 413.1474), λmax (EtOH) 210, 247, 254 sh, 292, 418, 504 sh, and 527 nm ($\log_{10}\varepsilon$ 3.97, 4.04, 4.02, 4.03, 3.53, 3.60 and 3.69); $\bar{\nu}$max 1735 (C=O/ester), 1645, 1620 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ Table 18; m/z 413 ($M^{+\cdot}$), 311 (M-OEt-C_4H_9), 266 (M-2OEt-C_4H_9). This compound gave a red solution in $CDCl_3$ which became orange upon addition of trifluoroacetic acid. The ^1H n.m.r. spectrum of the resulting solution showed the following peaks indicating the presence of two protonated species:

δ_H ($CDCl_3$/TFA) [200 MHz] 9.03 and 8.98 (2 overlapping doublets, 1H), 8.17 (s, 1H), 8.15 and 7.41 (2 singlets, 1H), 8.05 and 7.70 (2 doublets, 1H), 4.5-4.7 (m, 4H), 1.77 and 1.57 (2 singlets, 9H), and 1.4-1.5 (m, 6H); (coupling constant J 9-10 Hz).

(iii) A yellow band yielded the 1,2-di(ethoxycarbonyl)-[2.3.3]cyclazin-3-one (0.020 g, 10%).

(iv) A deep pink band, treated as for (ii), gave a purple solid (0.007 g, R1, 3%) which was identified as 1,3-di(ethoxycarbonyl)-4-oxo-4H-pyrido[2,1,6-de]quinolizinium-7-olate, (188), m.p. 145°C decomp., (Found: $M^{\cdot+}$ 341.0904. $C_{18}H_{15}NO_6$ requires $M^{\cdot+}$ 341.0899); λmax (EtOH) 218, 248, 270, 304, 326 sh, 402 and 535 nm ($\log_{10}\varepsilon$ 3.94, 3.87, 3.89, 3.91, 3.64, 3.62 and 3.63); $\bar{\nu}$max 1720 (C=O/ester), 1630, 1605 (C=O) cm^{-1}; δ_H($CDCl_3$) Table 18. This compound gave a purple solution in $CHCl_3$ which became orange upon addition of trifluoroacetic acid.

(v) A red band gave a red oil (0.027 g) that was shown by t.l.c. to be a mixture. Rechromatography (silica/EtOAc; preparative plate developed 4 x) gave the following bands: (a) an orange band that gave a red solid (0.013 g, R1A, 5%) identified as slightly impure 9-t-butoxy-1,3-di(ethoxycarbonyl)-4-oxo-4H-pyrido[2,1,6-de]-quinolizinium-7-olate, (191), [Found $(M+H)^+$ 414.1553 (FABMS). $C_{22}H_{24}NO_7$ requires (M+H) 414.1553]; λmax (EtOH) 212, 246, 270 sh, 304, 334, 384 sh, 402, 490 sh and 514 nm [qualitative only]; δ_H($CDCl_3$) Table 18; this compound gave a red solution in $CHCl_3$ which became orange upon addition

of trifluoroacetic acid;

(b) a purple-red band that gave a purple solid (0.006 g, R2, 3%) identified as 1,3-di(ethoxycarbonyl)-4-oxo-4H-pyrido[2,1,6-de]quinolizinium-9-olate, (189), m.p. 202°C decomp., (Found: $M^{+\cdot}$ 341.0865. $C_{18}H_{15}NO_6$ requires $M^{+\cdot}$ 341.0899); λmax (EtOH) 204, 244, 260 sh, 275 sh, 311, 321, 372 sh, 429, 522 sh and 547 nm ($\log_{10}\varepsilon$ 4.18, 4.30, 4.25, 4.18, 3.95, 3.95, 3.40, 3.89, 3.92 and 4.01); $\bar{\nu}$max 1720 (C=O/ester), 1620 (C=O) cm^{-1}; δ_H ($CDCl_3$) Table 18; this compound gave a deep red solution in $CHCl_3$ which became orange-red upon addition of trifluoroacetic acid; and (c) an orange-yellow band that gave an orange-brown oil (0.004 g). This material was shown to be a mixture of three components by t.l.c. and was not investigated further.

[Note 1] Strongly adsorbed material was recovered from the dry flash column by washing with ethanol and was shown by t.l.c. to contain more of the red and yellow oxidation products, thus suggesting that strongly polar intermediates in the oxidation process were still present when the reaction was stopped and that these were retained on the column. These additional amounts of products were separated, as described above, and are included in the reported yields.

E4.3.2 Isolation of two oxidative degradation products of the parent [3.3.3]cyclazine

1,3-Di(ethoxycarbonyl)[3.3.3]cyclazine (0.080 g, 0.26 mmol) was sublimed (at 170°C) into a vertical furnace tube under vacuum (0.001 torr) at 850°C, and the pyrolysate (a purple-red solid of metallic appearance) was collected in a cold trap (liquid nitrogen). The system was then allowed to cool under vacuum before admission of dry nitrogen gas delivered via a needle inserted through a rubber septum. The n.m.r. solvent, d^6-benzene (deoxygenated by refluxing under nitrogen) was then added to the pyrolysate by syringe via the septum. Despite precautions to exclude air in all subsequent manipulations, the pyrolysate slowly darkened to a brown colour, and the ^1H n.m.r. spectrum of the benzene solution showed no distinct resonances. The d^6-benzene n.m.r. sample was observed to develop a purple-blue colour (probably indicative of the cyclazine radical-cation) which was discharged by shaking the solution with aqueous sodium dithionite. The benzene layer was then pale yellow-green in colour and was observed to fluoresce under u.v. light (366 nm). At this stage the remainder of the pyrolysate in the f.v.p. cold trap was treated as above and the combined two-phase system of benzene and aqueous dithionite was extracted with dichloromethane (2 x 50 ml). The organic extract was filtered, dried and evaporated to give a greenish oily solid (0.015 g) which, by preparative t.l.c. on silica (developed with 1/. EtOAc, 2/. 5% EtOH

in EtOAc, 3/. 15% EtOH in EtOAc), gave two bands as described below in order of decreasing Rf.

(i) A fluorescent yellow band gave an orange-yellow solid (0.002 g) that was identified as 5H-pyrrolo[2,1,5-de]-quinolizin-5-one (37), (Found: $M^{+\cdot}$ 169.0522. $C_{11}H_7NO$ requires $M^{+\cdot}$ 169.0528), by t.l.c. comparison with an authentic sample and by ^1H n.m.r. spectroscopy; $\delta_H(CDCl_3)$ [200 MHz] 8.6 (d, 1H, H-6), 8.2 (d, 1H, H-8), 8.1 (d, 1H, H-3), 7.8 (dd, 1H, H-7), 7.6 (d, 1H, H-2), 7.3 (d, 1H, H-1), 7.2 (d, 1H, H-4). This n.m.r. spectrum is in agreement with the details published previously[6].

(ii) A yellow band that yielded a yellow solid (0.003 g) that was identified as 3H-pyrrolo[2,1,5-de]-quinolizin-3-one (34), (Found: $M^{+\cdot}$ 169.0523. $C_{11}H_7NO$ requires $M^{+\cdot}$ 169.0528), by t.l.c. comparison with an authentic sample and by ^1H n.m.r. spectroscopy, $\delta_H(CDCl_3)$ [200 MHz], δ8.15(dd, 1H, H-8), 8.10 (d, 1H, H-2), 7.97 (d, 1H, H-5), 7.80 (dd, 1H, H-6), 7.67 (dd, 1H, H-7), 7.48 (d, 1H, H-4), 7.29 (d, 1H, H-1); ($J_{1,2}$ 4.9; $J_{4,5}$ 9.7; $J_{6,7}$ 7.7; $J_{7,8}$ 8.2; $J_{6,8}$ 1.0 Hz). The n.m.r. spectrum is in agreement with that published previously[6].

E4.4 Miscellaneous Reactions

E4.4.1 Reaction of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with p-toluenediazonium tetrafluoroborate

The reaction carried out in the presence of DBU is described. A similar result was obtained when anhydrous potassium carbonate was used in place of DBU but preparative

t.l.c. was not attempted.

1,3-Di(ethoxycarbonyl)[3.3.3]cyclazine (0.075 g, 0.24 mmol) was dissolved in dry acetonitrile (10 ml) and DBU (0.073 g, 0.48 mmol) was added. The solution was then stirred at 0°C, whilst a chilled solution of the diazonium tetrafluoroborate (0.055 g, 0.26 mmol) in acetonitrile (2 ml) was added dropwise. The yellow-green colour of the cyclazine diester immediately darkened to a brown colour. After 21 h of stirring at 0°C, t.l.c. revealed that starting material was still present and a further amount (0.060 g) of the diazonium reagent was added. Stirring was continued for a further 1 h before the reaction was terminated by removal of the solvent in vacuo, to leave a brown oily residue which was shown by t.l.c. to contain a large number of minor components. Preparative t.l.c. [silica/CH_2Cl_2-Et_2O (5:1)] failed to give any significant amount of a characterisable product from the multicomponent mixture and thus no definite conclusion may be derived from these experiments.

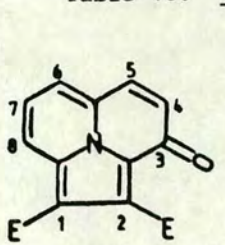
It was noted in small scale tests that effervescence (presumably N_2 evolution) occurred when the diazonium reagent was added to a solution of the [3.3.3]cyclazine diester whether or not a base was present.

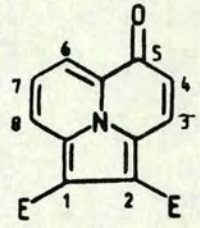
E4.4.2 Reaction of 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine with tetracyanoquinodimethane (TCNQ)

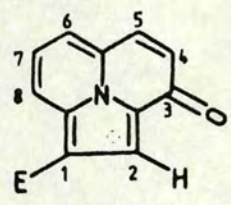
1,3-Di(ethoxycarbonyl)[3.3.3]cyclazine (0.051 g, 0.17 mmol) was refluxed under nitrogen with 7,7,8,8-tetracyanoquinodimethane [TCNQ] (0.034 g, 0.17 mmol) in dry

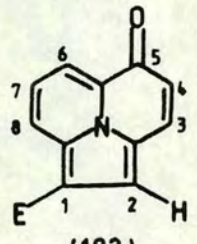
acetonitrile. After 1 h, the reaction mixture was cooled to room temperature, stirred for 24 h, and filtered to obtain a brown solid (0.069 g) which had precipitated. The solid was moderately soluble in dichloromethane or chloroform but unsuitable for chromatographic purification (t.l.c. showed a yellowish elongated spot near the base-line and one minor spot of high Rf). Since no suitable recrystallisation solvent could be found, the solid was extracted with ether in a Soxhlet apparatus, to remove more soluble impurities, and the ether-insoluble residue (0.038 g) was recovered and dried for analytical and spectroscopic investigation. It was tentatively identified as 6,6'-[p-phenylenebis(dicyanomethyl)]bis[1,3-di(ethoxy-carbonyl)pyrido[2,1,6-de]quinolizine] (206), m.p. 175°C decomp., (Found: C, 67.2; H, 4.2; N, 10.6; $M^{+\cdot}$ 824.2594 [FABMS in 3-nitrobenzyl alcohol] . $C_{48}H_{36}N_6O_8$ requires C, 69.9; H, 4.4; N, 10.2%; $M^{+\cdot}$ 824.2594); λmax (CH_2Cl_2) 248 sh, 292, 318 sh, 405, 458 sh and 480 nm ($\log_{10}\varepsilon$ 4.20, 4.88, 4.06, 4.57, 4.63, and 4.90); λmax (EtOH) 212, 222 sh, 290, 322, 402, 424 sh, 452 sh, 474 nm. [qualitative only]; $\bar{\nu}$max 1675 (C=O), 1610/1600 cm^{-1}; $\delta_H(CDCl_3)$ Table 19.

Table 16. ^{1}H n.m.r. spectra of compounds (33a), (181), (182) and (183)


(183)


(181)


(33a)


(182)

E = CO_2Et

δ/H[a)b)]	H-1	2	3	4	5	6	7	8	Coupling J/Hz
(183)[c)]	[1.47 4.58]	[1.42 4.44]	-	7.29(d)	7.91(d)	7.80(dd)	7.81(dd)	8.76(dd)	$J_{4,5}$ 9.9 $J_{6,7}$ indet. $J_{7,8}$ indet. e) $J_{6,8}$ indet. J_{gem} 7.1
(181)[c)]	[1.44 4.47]	[1.46 4.57]	8.26(d)	7.12(d)	-	8.56(dd)	7.94(dd)	8.84(dd)	$J_{3,4}$ 10.0 $J_{6,7}$ 7.6 $J_{7,8}$ 8.6 $J_{6,8}$ 1.1 J_{gem} 7.1
(33a)[c)]	[1.45 4.45]	8.47(s)	-	7.36(d)	7.94(d)	7.8	7.8	8.78(dd)	$J_{4,5}$ 9.9 $J_{6,7}$ indet. $J_{7,8}$ indet. e) $J_{6,8}$ indet. J_{gem} 7.1
(182)[d)]	[1.46 4.47]	7.98(s)	8.08(d)	7.08(d)	-	8.56(dd)	7.92(t)	8.87(dd)	$J_{3,4}$ 9.8 $J_{6,7}$ 7.6 $J_{7,8}$ 8.4 $J_{6,8}$ 1.2 J_{gem} 7.1

a In $CDCl_3$ b Values in parenthesis indicate substituent shift

c At 200MHz d At 80 MHz

e 2nd order effects

Table 17. Action of oxidants on 1,3-di(ethoxycarbonyl)[3.3.3]cyclazine

Reagent	Conditions	Products observed or obtained (by prep. t.l.c. or flash chromatography) 6,6'- (74)	3- (183)	5-(181)	R1	R2	Other
10% Pd-C	THF/reflux/air	-	Trace	Trace	Trace	Trace	-
Ag_2O	THF/reflux	15%[a]	Trace	Trace	Trace	Trace	S.M. (27%)
Bu_4NIO_4[b]	CH_2Cl_2/stir/r.t.	57%[a]	Trace	Trace	Trace	Trace	S.M. (10%)
"	aqs.THF/stir/r.t.	10%	Trace	Trace	Trace	Trace	S.M. (Trace)
$(C_5H_5NH)_2Cr_2O_7$[c]	CH_2Cl_2/stir/r.t.	63%[a]	-	-	-	-	S.M. (30%)
NaOCl	CH_2Cl_2/H_2O/TEBA[d] stir/r.t.	5%	3%		<1%[e]	Trace	-
CrO_3	ACOH/r.t.	-	8%	15%	4%[e]	N.I.	g)
H_2O_2	aq. THF/$MnCl_2$/ stir/r.t.	-	3%[f]	5%[f]	1%[f]	4%[f]	
H_2O_2	MeCN/$FeCl_3$/stir/r.t.	-	-	N.I.	-	-	h)

N.I. = Not Isolated; S.M. Starting Material (recovered)

a) Yields based on unrecovered [3.3.3]cyclazine diester (47a)

b) Tetrabutylammonium periodate (ref. 67)

c) Pyrdinium dichromate (ref. 68)

d) TEBA Benzyltriethylammonium chloride (a phase transfer catalyst)

cont.

Table 17 cont.

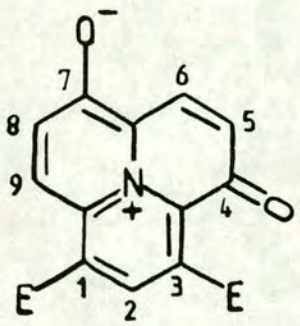
e) Obtained as an impure red solid; m/z 341; ^{1}H n.m.r. ($CDCl_3$) shows two AB systems and a singlet [δ9.01 (d)/7.50 (d); ^{3}J = 10.4 Hz; δ8.85 (d)/7.20 (d); ^{3}J = 9.9 Hz; 8.12 (s)]

f) Crude yield

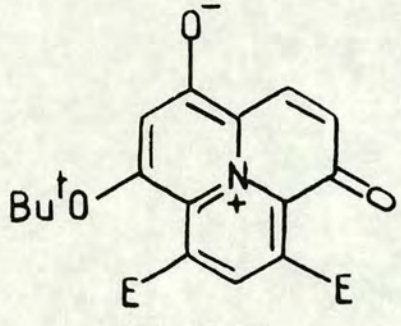
g) Also isolated was an orange-red oil; ^{1}H n.m.r. ($CDCl_3$) shows two AX spin systems [δ8.89 (d)/7.67 (d), ^{3}J = 8.9 Hz, δ8.25 (d)/6.88 (d), ^{3}J = 10.0 Hz]

h) Trace amount of a compound isolated that has a low Rf but does not match R1 or R2. Not isolated or characterised

Table 18. ^{1}H n.m.r. data (200 MHz) for R1, R1A, R2 and R2A in $CDCl_3$ (E = CO_2Et)

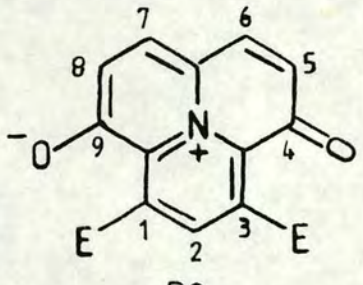


R1
(188)

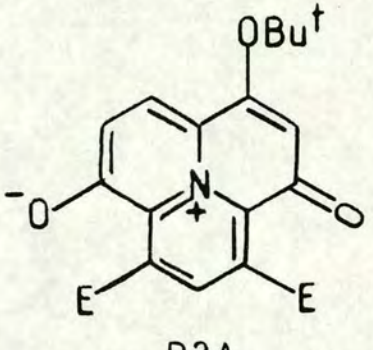


R1A
(191)

E = CO_2Et.



R2
(189)

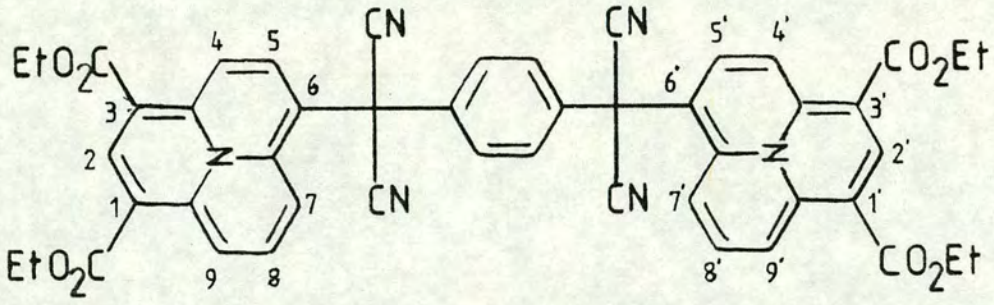


R2A
(190)

Compound	Position[b] δ/p.p.m.[a] 1(7)	2(8)	3(9)	4(1)	5(2)	6(3)	7(4)	8(5)	9(6)	Coupling constants J/Hz
(188)	[1.43 4.56]	8.11	[1.49 4.56]	-	7.20	8.85	-	7.51	9.00	$J_{5,6}$ 9.8; $J_{8,9}$ 10.4 Hz
(191)	[1,40 4.53]	7.50	[1.42 4.53]	-	7.14	8.76	-	7.01	(1.62)	$J_{5,6}$ 9.7 Hz
(189)	[1.43 4.55]	7.77	[1.43 4.55]	-	7.11	7.91	7.91	7.11	-	$J_{5,6}$ 9.7 Hz
(190)	[1.43 4.54]	7.65	[1.42 4.54]	-	6.79	(1.66)	8.42	7.10	-	$J_{7,8}$ 9.9 Hz

a) Values in parenthesis refer to protons in substituent groups
b) The unparenthesised numerals are those used in the discussion (ie. corresponding to starting material). Those given in parenthesis are the correct numbers according to the IUPAC rule that indicated hydrogen is given the lowest possible locant

Table 19. ^{1}H n.m.r. spectrum of the compound derived from the reaction of the [3.3.3]cyclazine diester with TCNQ



(206)

δ_H(CDCl$_3$)	m	Integral Ratio	No. of protons	Assignment
7.77	s	2	4H	H-aromatic
7.22	s	1	2H	H-2/2'
6.87	dd	1	2H	H-9/9'
6.54	d	1	2H	H-4/4'
6.28	d	1	2H	H-5/5'
6.14	t	1	2H	H-8/8'
4.69	dd	1	2H	H-7/7'
4.06	q	4	8H	CH_2(ester)
4.04	q			
1.22	t	6	12H	CH_3(ester)
1.20	t			

Coupling constants: $J_{4,5}$ 9.1; $J_{7,8}$ 8.5; $J_{8,9}$ 8.5; $J_{7,9}$ 1.4; J_{vic} 7.1 Hz

E5 Investigation of flash vacuum pyrolysis as a route to [3.3.3]cyclazines

E5.2 F.V.P. as a route to aza[3.3.3]cyclazines

E5.2.1 Attempts to generate 1-aza[3.3.3]cyclazines

4H-Quinolizin-4-ylidenemalononitrile

This compound was prepared by the method of Mathur[92].

Starting from 4-chloroquinolizinylium perchlorate (2.64 g, 0.01 mol) and sodiomalononitrile, 4H-quinolizin-4-ylidene malononitrile was obtained as golden yellow needles (1.5 g, 78%), m.p 211-213°C (lit.[37] m.p. 210-212°C).

Attempt to cyclise 4H-quinolizin-4-ylidenemalononitrile in solution

A solution of 4H-quinolizin-4-ylidenenalononitrile (0.55 g, 3.0 mmol) in 1,2,4-trichlorobenzene (25 ml) [b.p. 214°C] was refluxed under nitrogen. After 5 h, t.l.c. showed that no reaction had taken place and the solution was filtered and evaporated under reduced pressure. Trituration of the recovered material with ether gave a yellow-brown solid (0.48 g) which was shown by infrared spectroscopy and t.l.c. to be starting material (87%).

Flash vacuum pyrolysis of 4H-quinolizin-4-ylidenemalononitrile

The quinolizinylidene compound (0.94 g, 4.9 mmol) was sublimed (180°C) through a silica pyrolysis tube held at 800°C and evacuated to 0.005 mmHg. The pyrolysis products were collected in a U-trap cooled in liquid nitrogen and appeared as a blue film deposited on the glass.

The apparatus was allowed to cool under vacuum before admitting air and the pyrolysate was then removed from the trap by dissolution in dichloromethane. The solvent was evaporated and the residue (shown by t.l.c. to contain at least five components) was subjected to flash column chromatography (silica) eluting with dichloromethane-ethyl acetate to give the following fractions.

(i) A yellow band yielded a yellow solid (FVP1) which was recrystallised from light petroleum (b.p. 60-80°C)-ethyl acetate to give pale yellow prisms (0.020 g, 2%), m.p. 192-195°C decomp., tentatively identified as 8-cyano-5-(cyanomethyl)quinoline (214) containing a small amount of 2-cyano-8-(cyanomethyl)quinoline (216), (Found: $M^{+\cdot}$ 193.0639. $C_{12}H_7N_3$ requires $M^{+\cdot}$ 193.0640); $\bar{\nu}$max 2250/2230/2220 (C≡N) cm^{-1}; $\delta_H(CDCl_3)$ Table 21.

(ii) A pale blue band yielded a light grey-blue solid (FVP2) which was recrystallised from ethyl acetate to give 2-cyano-5-(cyanomethyl)quinoline (213), (0.080 g, 8%) as pale blue needles, m.p. 158-161 °C; (Found: $M^{+\cdot}$ 193.0640. $C_{12}H_7N_3$ requires $M^{+\cdot}$ 193.0640); $\bar{\nu}$max 2250/2240 (C≡N) cm^{-1}; λmax [EtOH] 208, 240, 291, 318 and 332 nm ($\log_{10}\varepsilon$ 4.62, 4.89, 3.72, 3.55 and 3.42); δ_H/δ_C Tables 21 and 23; m/z 193 ($M^{+\cdot}$, 100%), 166 ($M^{+\cdot}$-HCN), 139 ($M^{+\cdot}$-2HCN).

(iii) A trace amount of a brown oil obtained from a yellow band was not characterised further.

(iv) A blue band yielded a dark grey-blue solid (FVP3) which was recrystallised from chloroform-ethyl acetate to give 5-(dicyanomethyl)quinoline (210) [0.172 g, 18%] as

blue needles, m.p. 186-189°C, (Found: C, 74.3; H, 3.8; N, 21.4; $M^{+\cdot}$ 193.0638. $C_{12}H_7N_3$ requires C, 74.6; H, 3.6; N, 21.8%; $M^{+\cdot}$ 193.0640); $\bar{\nu}$max 2175 (C≡N), 2130 (C≡N) cm^{-1}; λmax refer to Table 20; δ_H/δ_C Table 21 and 22; m/z 193($M^{+\cdot}$,100%), 166($M^{+\cdot}$-HCN), 139($M^{+\cdot}$-2HCN), 128[$M^{+\cdot}$-CH(CN)$_2$].

(v) An orange-brown band yielded a trace amount of a red solid which was shown by t.l.c. to contain at least three components including some starting quinolizin-4-ylidenemalononitrile compound.

[Note] The column was heavily stained at the top implying that decomposition products were also present.

An approach to the unambiguous synthesis of 5-(dicyanomethyl)quinoline

5-Nitroquinoline

This compound was obtained from quinoline in 34% yield by the method of Fieser and Hershberg[93].

δ_H($CDCl_3$, 80 MHz) 7.62 (dd, 1H, H-2, J 8.6/4.4 Hz), 7.78 (t, 1H, H-7, J 8.1 Hz), 8.3-8.5 (m, 2H), 8.9-9.1 (m, 2H).

5-Aminoquinoline

This compound was obtained from 5-nitroquinoline (12.7 g, 0.07 mol) by a procedure similar to that of Fieser and Hershberg[92]. Hydrogenation over Adams catalyst (0.14 g) for 7 h, being incomplete, was followed by further hydrogenation over 10% Pd-C/1 atm. hydrogen for 20 h. When absorption of hydrogen was complete, the ethanol solution was stirred with charcoal, filtered, and evaporated to give a reddish oil which distilled at

80-85°C/0.05 mmHg in a Kügelröhr to give the amine as a yellow solid (5.65 g, 54%). A small amount of the amine was recrystallised from light petroleum (b.p. 60-80°C)-ethyl acetate to give pale yellow needles, m.p. 109-112°C (lit.[92] m.p. 108-110°C), δ_H (d^6-dmso, 200 MHz) 5.94 (br. s, 2H, NH_2), 6.70 (dd, 1H, H-6), 7.18 (dt, 1H, H-8), 7.34 (dd, 1H, H-3), 7.41 (dd, 1H, H-7), 8.50 (ddd, 1H, H-4), 8.76 (dd, 1H, H-2), ($J_{2,3}$ 4.1; $J_{2,4}$ 1.7; $J_{3,4}$ 8.6; $J_{6,7}$ 7.6; $J_{6,8}$ 1.0; $J_{7,8}$ 8.3 Hz).

5-Iodoquinoline

5-Aminoquinoline (5.65 g, 0.004 mol) was dissolved in a mixture of conc. sulphuric acid (6 ml, 0.11 mol) and water (13 ml) in a 100 ml conical flask. While maintaining the temperature below 10°C (more normally 0 to 5°C) a chilled solution of sodium nitrite (2.67 g, 0.04 mol) in water (13 ml) was added slowly, until a slight excess was present as denoted by testing a small aliquot of the solution with KI/starch indicator paper. A solution of potassium iodide (6.0 g, 0.04 mol) in water (7 ml) was then added slowly, with stirring. Nitrogen gas was evolved and the solution darkened in colour. After 15 h, aqueous (satd.)sodium metabisulphite was added to destroy any iodine that had been formed, and the solution was made slightly alkaline with 10% sodium hydroxide. The solution was filtered and the filtrate was extracted with dichloromethane (3 x 300 ml) which was washed once with water (800 ml) and dried over $MgSO_4$. Evaporation of the dried solvent gave a dark brown solid which was sublimed

(180°C/0.01 mmHg) to give slightly impure 5-iodoquinoline (0.40 g) as an orange-yellow solid, m.p. 95°C (lit. 100°C)[94]; δ_H($CDCl_3$, 80 MHz) 7.3-7.6 (m, 2H, H-3/6), 8.12 (2 x d, 2H, H-7/8), 8.38 (dd, 1H, H-4), 8.88 (dd, 1H, H-2); ($J_{2,3}$ 4.2; $J_{2,4}$ 1.6; $J_{3,4}$ 8.8; $J_{6,7}/J_{6,8}$ and $J_{7,8}$ indeterminate; m/z 255 ($M^{+\cdot}$).

The mass spectrum had a peak at m/z 144, suggesting that a small amount of 5-hydroxyquinoline could have been present as an impurity, probably formed by hydrolysis of the diazonium salt.

Transition metal catalysed reactions of 5-iodoquinoline with sodiomalononitrile

(a) $PdCl_2(PPh_3)_2$ as the catalyst

This procedure was based on the work of Takahashi et al[77].

The anion of malononitrile was generated under a dry nitrogen atmosphere by reaction of sodium hydride (0.043 g, 0.9 mmol) with malononitrile in dry THF (4 ml) at 50°C for 0.75 h. To this solution was added 5-iodoquinoline (0.200 g, 0.8 mmol) and a catalytic amount of $PdCl_2(PPh_3)_2$[95] (0.008 g). The mixture was stirred and refluxed but, after 7 h, no product was detected by t.l.c.; DMF (1 ml) was then added to enhance the reaction but, after a further 2 h refluxing, no product was observable by t.l.c..

The reaction was worked up by adding the mixture to water (5 ml) and making the solution firstly acidic (to pH 3) with dilute hydrochloric acid, and extracting

with diethyl ether, and then by making the solution basic (pH 8-9) and once again extracting with ether. Both extracts yielded small amounts of crude 5-iodoquinoline (total recovery 0.035 g) but no reaction product was obtained.

(b) CuI as the catalyst

This procedure was based on the work of Suzuki et al[78].

Working under a dry nitrogen atmosphere, a solution of malononitrile (0.132 g, 2.0 mmol) in dry HMPA (1.5 ml) was added dropwise to a dispersion of sodium hydride (0.100 g, 4.3 mmol) in HMPA (1.0 ml). After 15-20 min., a solution of 5-iodoquinoline (0.250 g, 1 mmol) in HMPA (1 ml) was added along with cuprous iodide [Note 1]. (0.381 g, 2.0 mmol). The mixture was stirred with gradual heating to 115-120°C, and refluxed for 9 h, after which it was cooled and quenched with dilute hydrochloric acid (2N, 3 ml). The acidic solution was extracted with diethyl ether (4 x 15 ml), basified with sodium hydroxide (to pH 8) and once again extracted with ether (4 x 15 ml). Both extracts were dried and evaporated but the residue from the basic extract was small and yielded no characterisable product.

The residue of the acidic extract gave a trace amount of a blue oil, t.l.c. of which showed a blue spot identical with that of the fvp product (FVP3). Attempts to crystallise this blue oil by trituration failed and even after preparative t.l.c. (silica/EtOAc), the blue oil

(0.003 g) was once again obtained. The ^1H n.m.r. and uv spectra [Note 2] of the oil showed peaks corresponding to those in the spectra of FVP3 but impurity peaks were also present.

Note 1. The CuI was dried at 110°C for 16 h.

Note 2. δ_H ($CDCl_3$, 80 MHz) 9.2 (d), 8.3 (dd), 7.3-8.2 (m), 1.4 (s); λmax (EtOH) [qualitative only] 221, 266, 273, 280, 301, 306, 314, 432 and 586 nm.

Flash vacuum pyrolysis of 5-methylquinolizine-4-ylidene-malononitrile

A sample of the title compound, which had been synthesised previously in these laboratories[92], was flash vacuum pyrolysed at 800°C under high vacuum (0.005 mmHg).

The pyrolysate appeared first as a faint blue colour which quickly darkened to a dark brown. Chloroform was added to the pyrolysate, the resulting suspension was filtered, and the filtrate was evaporated under reduced pressure to give a dark residue that showed only immobile dark material on t.l.c. (silica/EtOAc).

Fvp of ethyl 4H-quinolizin-4-ylidenecyanoacetate

Preparation of title compound

The title compound was prepared from 4-chloroquinolizinylium perchlorate (2.64 g, 0.010 mol) and ethyl cyanoacetate (2.26 g, 0.020 mol) according to the method of Mathur[92], and was obtained as golden-brown needles from ethanol (2.00 g, 83%), m.p. 153-155°C (lit.[92] m.p. 154-156°C).

F.v.p. of ethyl 4H-quinolizin-4-ylidenecyanoacetate

Ethyl 4H-quinolizin-4-ylidenecyanoacetate (0.900 g, 4.0 mmol) was sublimed through a pyrolysis tube held at 800°C and evacuated to 0.005 mmHg. The pyrolysis system was allowed to cool and the orange-red solid which had collected in the cold trap was removed by dissolution in dichloromethane. Flash column chromatography on alumina (10% deact. neutral), eluting with various combinations of CH_2Cl_2-$CHCl_3$-EtOAc removed two bands.

(i) A yellow band yielded a brown solid (0.025 g, 3%) identified as starting material.

(ii) A broad orange band yielded an orange solid which was recrystallised from toluene-methanol to give 2-cyano-1H-pyrrolo[2,1,5-de]quinolizin-1-one (26c) (0.55 g, 71%) as orange needles, m.p. 261-264°C (lit.[6] m.p. 262-264°C), i.r. and n.m.r. spectra identical with those of the specimen reported[6] previously.

E5.2.2 Attempts to generate 2-aza[3.3.3]cyclazines

(i) Reaction of 4-chloroquinolizinylium perchlorate with ethyl isocyanoacetate

The anion of ethyl isocyanoacetate (1.13 g, 0.01 mol) was generated[22] in THF (20 ml) under dry nitrogen by reaction of the ester with sodium hydride (0.24 g, 0.01 mol) at room temperature. The clear yellow solution was then cooled to 0°C and 4-chloroquinolizinylium perchlorate (1.32 g, 5.0 mmol) was added in small aliquots which gave rise to a red-purple colour. The stirred mixture was allowed to come to room temperature and stirred under dry

nitrogen for 24 h, after which it had become very dark. The THF was evaporated and the residue was taken up in water, which was then extracted with dichloromethane (3 x 200 ml) and the dark extract was washed once with water and dried over $MgSO_4$. Evaporation gave a brown oil, shown by t.l.c. to contain several components, including a major amount of dark immobile material. Flash column chromatography on alumina (neutral, 6% deact.) and preparative t.l.c. failed to give a sufficient amount of any product for characterisation.

(ii) Reaction of 4-chloroquinolizinylium perchlorate with p-tosylmethyl isocyanide (TosMIC)

Under a dry nitrogen atmosphere, LDA (0.404 g, 4 mmol) was generated[38] at -5°C in dry THF (4 ml). The flask was then cooled to -78°C prior to addition of TosMIC (0.780 g, 4 mmol) in dry THF (15 ml), which gave a clear orange-brown colour after 20 min. at this temperature. Whilst maintaining the temperature at -78°C, 4-chloroquinolizinylium perchlorate (0.53 g, 2.0 mmol) was added in small aliquots. After complete addition, the solution had become clear purple-red but a small aliquot, removed for t.l.c. purposes, darkened rapidly as it warmed to room temperature, revealing only decomposition products on t.l.c..

The main reaction mixture was stirred for a further 6 h at -78°C when no further reaction appeared to be taking place. The reaction flask was stored in the freezer but even this treatment did not prevent decomposition and the

contents of the flask darkened substantially. In an attempt to salvage something from this experiment, the reaction mixture was subjected to flash column chromatography (silica), when elution with dichloromethane-diethyl ether removed several fractions which yielded small amounts of materials.

(i) An orange band yielded an orange-brown solid (0.080 g) which was identified by ^{1}H n.m.r. and i.r. spectroscopy as an impure specimen of TosMIC, $\bar{\nu}$max 2150 (-N≡C), 1595 cm^{-1}.

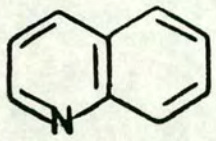
(ii) An orange band gave a red-brown oil (0.035 g) that could not be crystallised by trituration with Et_2O. This material was not characterised.

(iii) A red band yielded a hygroscopic red solid (0.099 g) which could not be characterised due to its lack of purity, but did not show an isocyano band (ca. 2150 cm^{-1}) in its infrared spectrum.

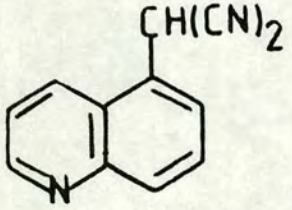
(iv) A trace amount of a pale orange solid was shown to be a mixture by t.l.c..

(v) A crude brown oil (0.200 g) obtained from a blue band showed only dark immobile material when re-examined by t.l.c..

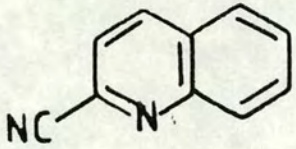
Table 20. U.V. spectroscopic data for the quinoline series of isolated compounds



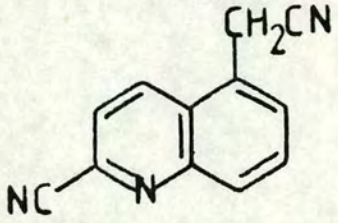
(230)



(210)
FVP3



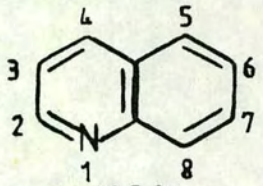
(231)



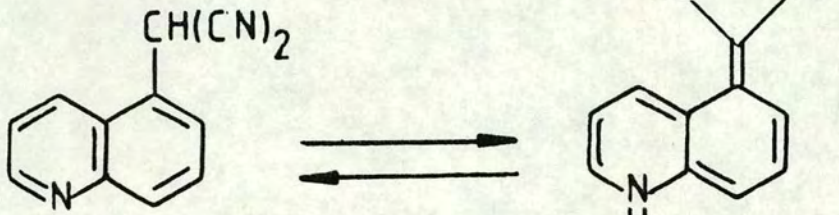
(213)
FVP2

Compound	U.V. Solvent	λ_{max}/nm ($\log_{10}\varepsilon$)				
(230)	EtOH		230 (4.4)	276 (3.6)	301 (3.5)	314 (3.6)
FVP3 (210)	EtOH[a]	218 (4.6)	233 (4.2)	281 (4.0)	301 (3.9)	315 (3.7)
FVP3	THF			273 (3.9)	301 (3.6)	314 (3.6)
FVP3	CH_2Cl_2 (EtOH free)		229 (4.3)	274 (3.9)	302 (3.6)	316 (3.8)
(231)	EtOH[b]			295 (3.6)	320 (3.4)	330 (3.3)
FVP2 (213)	EtOH	208 (4.6)	240 (4.9)	291 (3.7)	318 (3.6)	332 (3.4)

a Also visible is a broad band, λmax 593 nm (3.0) when a concentration of 9.83×10^{-4} $mol.l^{-1}$ is used (10 x concentration used for other calculations).
b Literature data (N. Hata and T. Saito, Bull.Chem.Soc.Jap., 1974, 47, 942.)

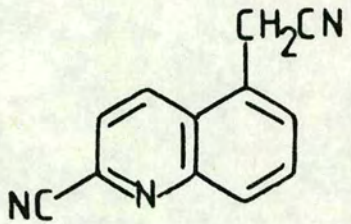


(230)

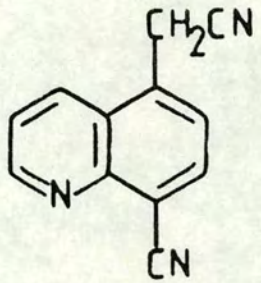


(210A)
FVP3

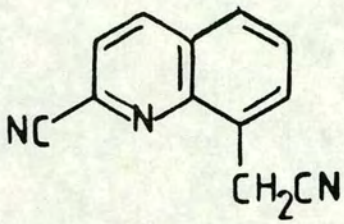
(210B)



(213)
FVP2



(214)
FVP1A



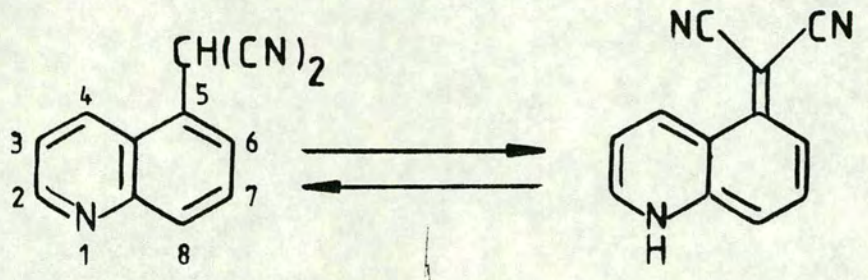
(216)
FVP1B

Table 21. Proton n.m.r. spectra of the Quinoline series

δ/H	Solvent	H-2	H-3	H-4	H-5	H-6	H-7	H-8	Coupling constants, J/Hz
(230)	CCl_4 [a]	8.82	7.31	8.05	7.73	7.46	7.65	8.05	$J_{2,3}$ 4.2; $J_{2,4}$ 1.8; $J_{3,4}$ 8.2; $J_{4,8}$ 0.8; $J_{5,6}$ 8.2; $J_{5,7}$ 1.5; $J_{5,8}$ 0.7; $J_{6,7}$ 6.9; $J_{6,8}$ 1.2; $J_{7,8}$ 8.6 Hz
(230)	$CDCl_3$ [b]	8.82 (dd)	7.23 (dd)	7.98 (ddd)	7.66 (m)	7.41 (ddd)	7.60 (ddd)	8.05 (m)	$J_{2,3}$ 4.2; $J_{2,4}$ 1.8; $J_{3,4}$ 8.3; $J_{4,8}$ 0.7; $J_{5,6}$ 8.1; $J_{5,7}$ 1.6 $J_{5,8}$ 0.8; $J_{6,7}$ 6.9; $J_{6,8}$ 1.2; $J_{7,8}$ 8.5 Hz
(230)	d^6-acetone [c]	8.90	7.47	8.29	7.92	7.54	7.74	8.07	$J_{2,3}$ 4.2; $J_{3,4}$ 8.3; $J_{5,6}$ 8.0; $J_{6,7}$ 6.8; $J_{7,8}$ 8.6 Hz
FVP3 (210)	$CDCl_3$ [b]	9.07 (dd)	7.62 (dd)	8.29 (m) [d]	(5.54) (s)	7.7-7.9 ⟵(m)⟶		8.33 (m) [d]	$J_{2,3}$ 4.3; $J_{2,4}$ 1.5; $J_{3,4}$ 8.6 Hz; other couplings obscured. (J indeterminate)
FVP3 (210)	d^6-acetone [b]	9.08 (dd)	7.77 (dd)	8.69 (br.d)	(6.7) (br.s)	7.8-8.0 ⟵(m)⟶		8.24 (br.d)	$J_{2,3}$ 4.1; $J_{2,4}$ 1.2; $J_{3,4}$ 8.7 Hz; $J_{6,7}/J_{6,8}/J_{7,8}$ indeterminate
FVP2 (213)	$CDCl_3$ [b]	-	7.82 (d)	8.41 (dd)	(4.16) (s)	7.7-7.9 ⟵(m)⟶		8.20 (ddd)	$J_{3,4}$ 8.7; $J_{6,7}$ indet.; $J_{6,8}$ 2.2; $J_{4,8}$ ~0.9 Hz other couplings indeterminate
FVP1A (214)	$CDCl_3$ [b]	9.06 (dd)	7.69 (dd)	8.58 (dd)	(4.49) (d)	7.96 (dt)	8.02 (d)	-	$J_{2,3}$ 4.2; $J_{2,4}$ 1.7; $J_{3,4}$ 8.5; $J_{6,7}$ 7.5; $J_{CH_2C_6}$ ~0.9 Hz
FVP1B (216)	$CDCl_3$ [b]	-	7.77 (d)	8.35 (d)	7.9 (br.d)	7.7 (dd)	8.1 (dd)	(4.44) (s)	$J_{3,4}$ 8.4; $J_{5,6}$ ~8; $J_{6,7}$ ~ 7 Hz; other couplings indeterminate

a Spectrum from literature (ref. F.Taddei et al, Org.Mag.Res., 1975, 7, 451)
b 200 MHz proton n.m.r. spectrum. Substituent groups are shown in parenthesis
c Spectrum from literature (ref. P.J. Black and M.L. Heffernan, Aust.J.Chem., 1964, 17, 558)
d possibly mt

Table 22. ^{13}C n.m.r. data for compound FVP3

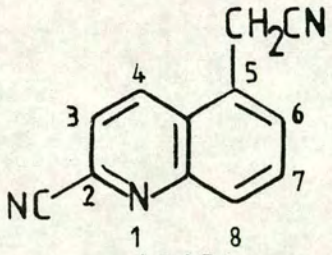


(210A) (210B)

a) 90.56MHz ^{13}C n.m.r.
b) 50.32MHz ^{13}C n.m.r.

$\delta(CDCl_3)$[a]		Assignment	$\delta(d^6\text{-acetone})$[b]		Assignment
25.8		$\underline{C}H(CN)_2$	24.9		$\underline{C}H(CN)_2$
111.1	q	2 x C≡N	112.1		2 x C≡N
121.9	q	C-5	121.5		C-3
122.5		C-3	124.0	q	C-4a
124.6	q	C-4a	126.3		C-6
127.6		C-6	128.5		C-8
128.9		C-8	130.0		C-7
129.7		C-7	131.1		C-4
133.3		C-4	131.2		C-5
148.7	q	C-8a	147.9	q	C-8a
151.3		C-2	150.4		C-2

Table 23. ^{13}C n.m.r. data for compound FVP2



(213)

FVP2

δ/p.p.m. ($CDCl_3$) a),b)	DEPT	Assignment
21.1	-	$\underline{C}H_2(CN)$
123.8	+	sp^2-CH
129.8	+	"
130.8	+	"
131.0	+	"
132.4	+	"

δ/p.p.m. ($CDCl_3$) a),c)	Assignment
116.5	C≡N
117.0	C≡N
123.9	sp^2-C
126.4	2 x sp^2C
148.5	sp^2C_{2a}

a) 50.32 MHz n.m.r..

b) DEPT spectrum $p\phi = 3\pi/4$ CH(+), CH_3(+), CH_2(-); quaternaries not visible.

c) Quatgen ^{13}C n.m.r. spectrum (quaternaries visible only).

U.V. SPECTRUM - COMPARISON OF COMPOUND FVP3(210) WITH QUINOLINE IN ETHANOL.

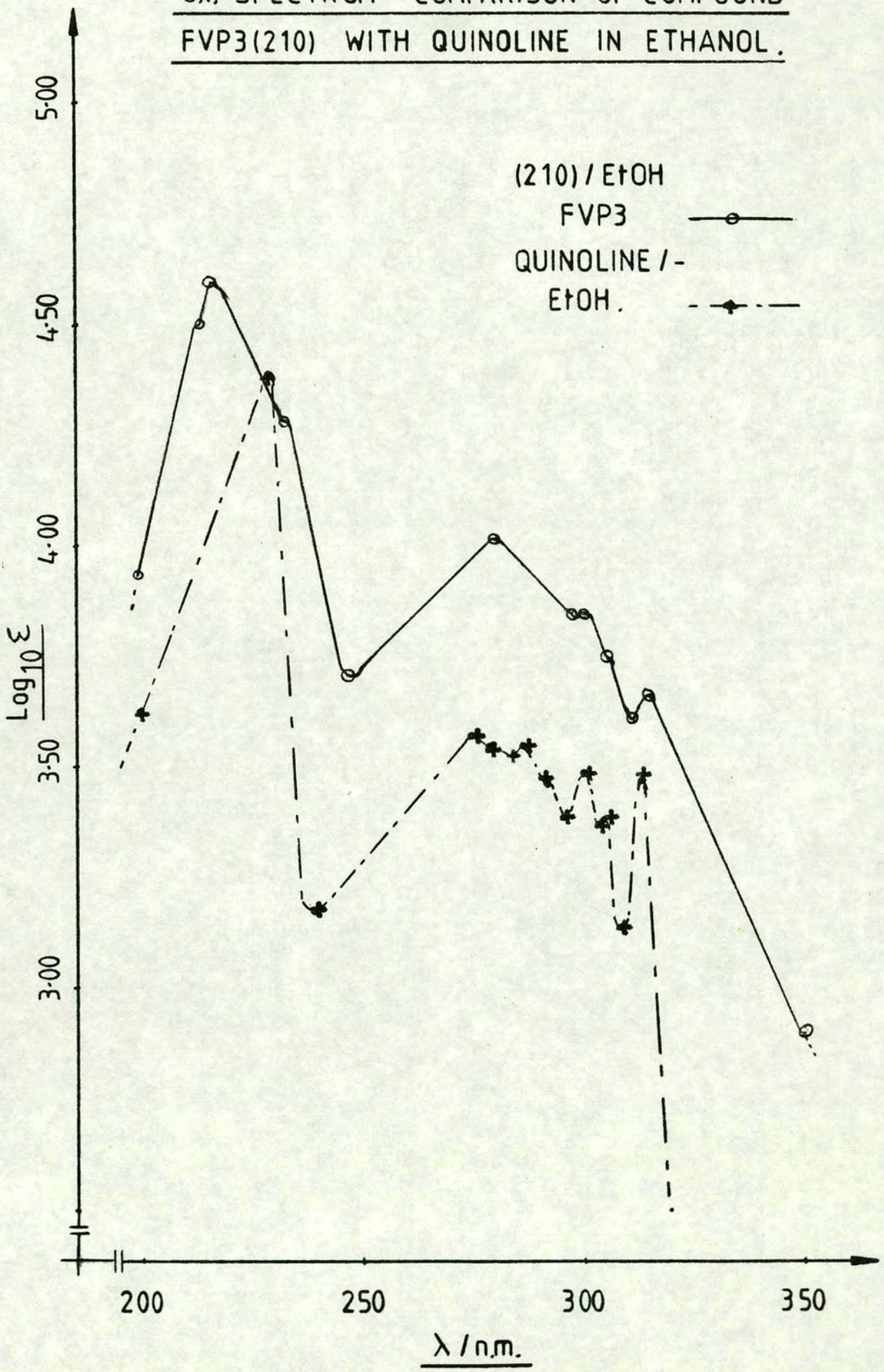


FIG. 4

U.V. SPECTRUM - COMPARISON OF COMPOUND FVP3(210) IN THF AND CH_2Cl_2.

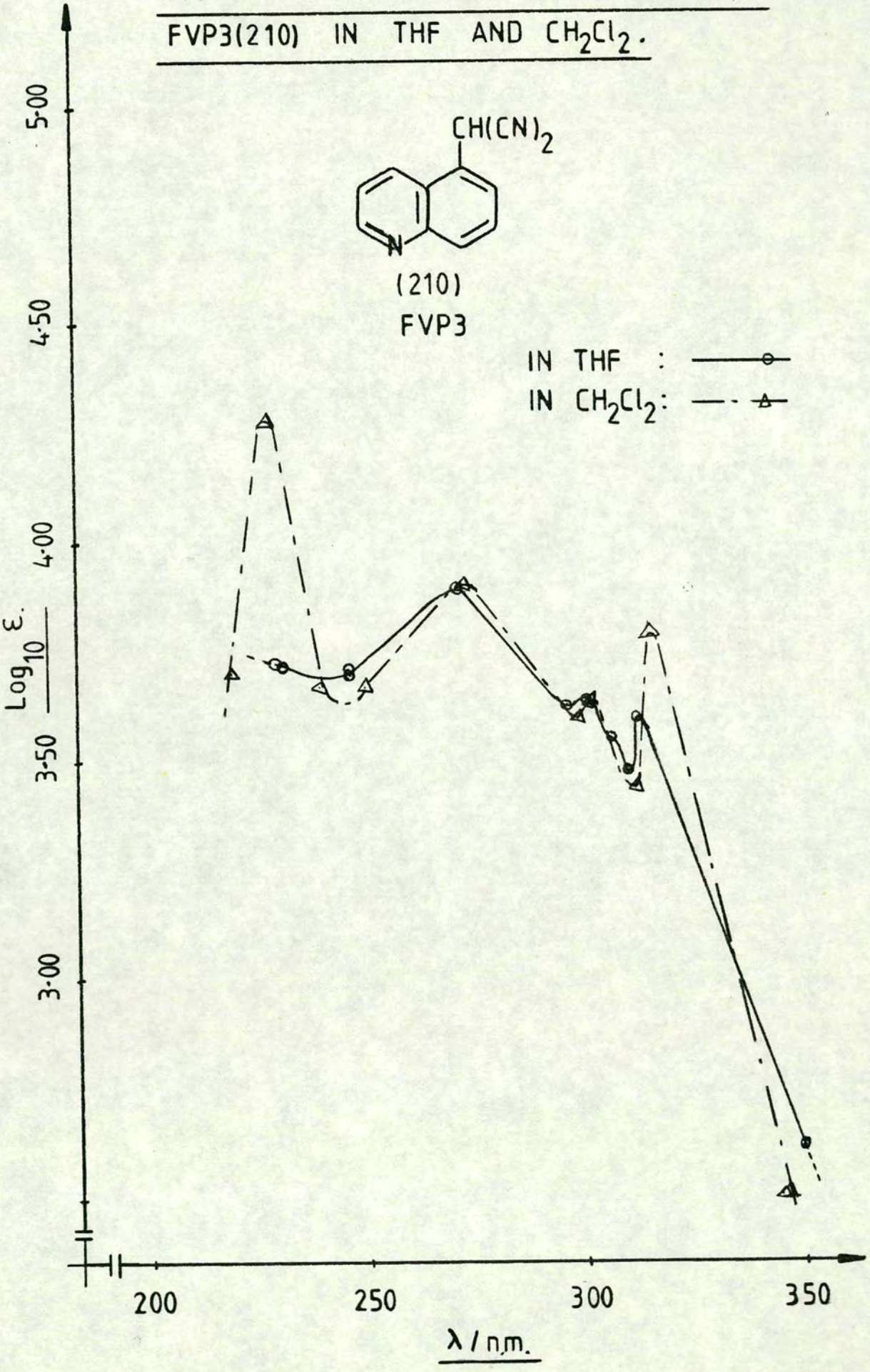


FIG. 5

U.V. SPECTRUM - COMPARISON OF COMPOUND FVP2 (213) WITH 2-CYANOQUINOLINE IN ETHANOL.

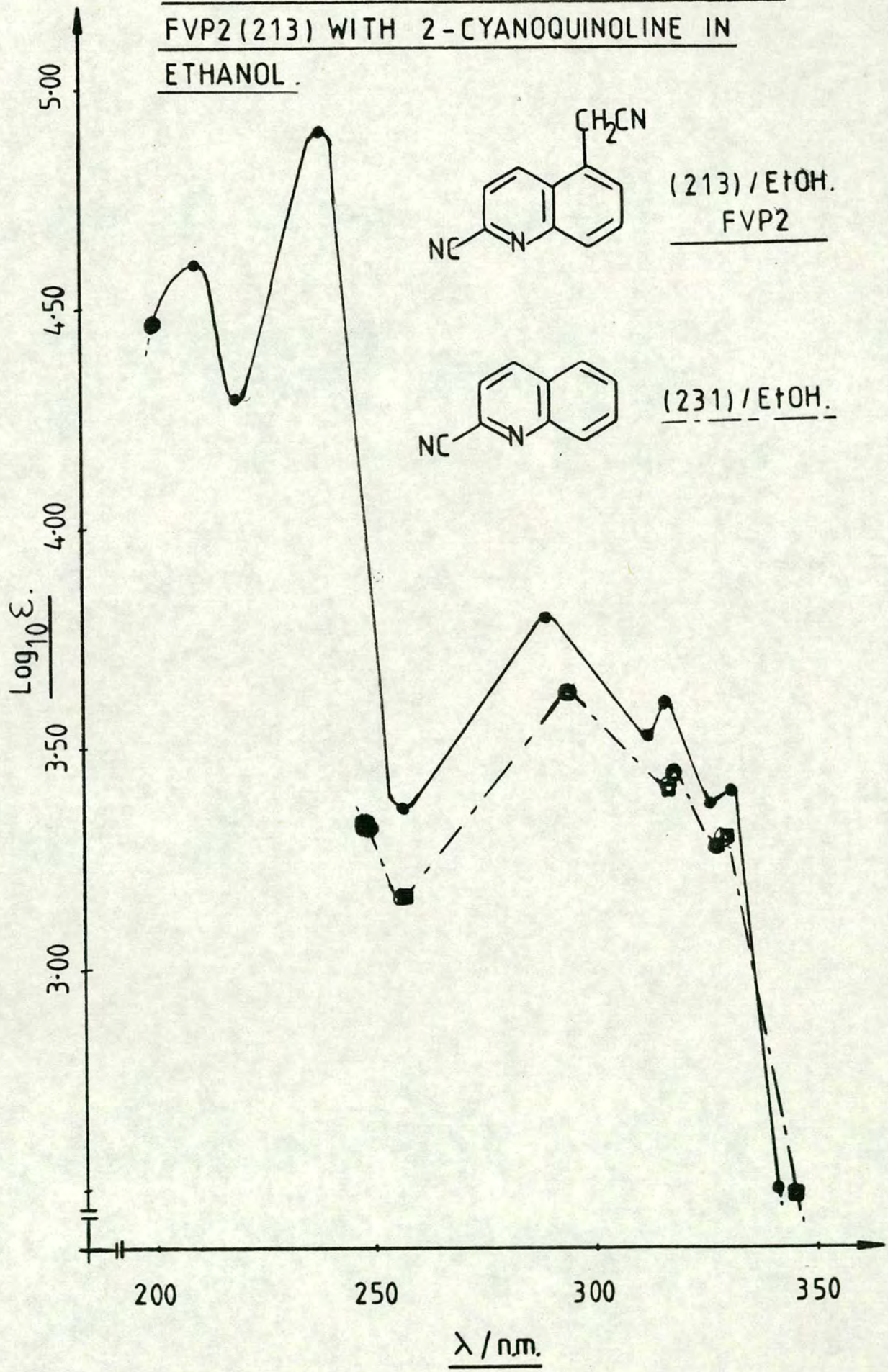


FIG. 6

E6 Preparation of [2.3.3]cyclazinones

E6.2 Synthesis of di(ethoxycarbonyl)[2.3.3]cyclazin-3- and -5-ones

1-Hydroxyquinolizinylium bromide

This compound was prepared by the method of Fozard and Jones[81].

Starting from 1,2,3,4-tetrahydro-1-oxoquinolizinylium bromide (6.17 g, 0.03 mol), 1-hydroxyquinolizinylium bromide monohydrate was synthesised (3.80 g, 59%) as a colourless crystalline solid, m.p. 182-184°C (lit.[81] m.p. 184-185°C).

3-Hydroxyquinolizinylium bromide

The title compound was prepared in 23% yield by the method of Duke, Fozard and Jones[80].

Starting from 2-pyridine carbaldehyde (21.40 g, 0.20 mol), the title compound was obtained (10.00 g) as buff crystals, m.p. 251-254°C (lit.[80] m.p. 252-254°C).

Diethyl 3-oxo-3H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (183)

Under a dry N_2 gas atmosphere, 3-hydroxyquinolizinylium bromide (0.50 g, 2.2 mmol), 9,10-phenanthraquinone (0.47 g, 2.2 mmol) and diethyl acetylenedicarboxylate (0.57 g, 3.3 mmol) were stirred together in dry acetonitrile (35 ml). Anhydrous sodium carbonate (0.47 g, 4.4 mmol) was added, and the solution was stirred and heated under reflux for 4 h. The reaction mixture was cooled and filtered and the solvent was removed *in vacuo*. The residue (1.2 g) was then subjected to flash chromatography (silica), eluting

with ether/dichloromethane which removed the following bands:

(i) an orange band that gave recovered 9,10-phenanthraquinone (0.096 g) and

(ii) an orange-yellow band that gave a yellow solid which was recrystallised from ethyl acetate to give diethyl 3-oxo-3H-pyrrolo[2,1,5-de]-1,2-dicarboxylate (183) (0.27 g; 39%) as yellow needles, m.p. 190-192°C. (Found: C, 65.0; H, 4.8; N, 4.5. $C_{17}H_{15}NO_5$ requires C, 65.2; H, 4.8; N, 4.5%); $\bar{\nu}$max 1735, 1700 (C=O, ester) and 1610 (C=O, ring) cm^{-1}; n.m.r. $\delta_H(CDCl_3)$ Table 16 (text); m/z 313 ($M^{+\cdot}$), 169 (100%).

Diethyl 5-oxo-5H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (181)

1-Hydroxyquinolizinylium bromide monohydrate (0.50 g, 2.0 mmol), diethyl acetylenedicarboxylate (0.52 g, 3.0 mmol) and 9,10-phenanthraquinone (0.43 g, 2.0 mmol) were stirred together in dry acetonitrile (30 ml) under a dry nitrogen atmosphere. Anhydrous sodium carbonate (0.43 g, 4.0 mmol) was then added, and the mixture was stirred and refluxed for 4 h. After being cooled and filtered the solution was evaporated and the dark-brown oily residue (1.4 g) was subjected to flash column chromatography (silica), eluting with diethyl ether/dichloromethane. An orange-green band yielded an orange-yellow solid which was vacuum sublimed (130-180°C/0.2 mmHg) and recrystallised from ethyl acetate to give diethyl 5-oxo-5H-pyrrolo[2,1,5-de]-quinolizine-1,2-dicarboxylate (181) (0.20 g, 32%) as yellow needles,

m.p. 116-118°C (Found: C, 65.0; H, 4.8; N, 4.8. $C_{17}H_{15}NO_5$ requires C, 65.2; H, 4.8; N, 4.5%); $\bar{\nu}$max 1705 (C=O , ester), 1647 (C=O, ring) cm^{-1}; λmax (EtOH) 222, 244, 258, 278 sh, 290, 298 sh, 336 sh, 352, 444 sh and 472 nm ($\log_{10}\varepsilon$ 4.28, 4.29, 4.27, 4.29, 4.35, 4.33, 3.42, 3.51, 4.08 and 4.37); $\delta_H(CDCl_3)$ Table 16 (text); m/z 313 ($M^{+\cdot}$), 240 (100%).

E6.3 Reactions of 1- and 3-hydroxyquinolizinylium salts with ethyl propiolate in the presence of phenanthraquinone

Ethyl 3-oxo-3H-pyrrolo[2,1,5-de]quinolizine-1-carboxylate

The procedure was essentially as described for the 1,2-diester. 3-Hydroxyquinolizinylium bromide (o.50 g, 2.2 mmol), ethyl propiolate (0.32 g, 3.3 mmol) and 9,10-phenanthraquinone (0.47 g, 2.2 mmol) were refluxed for 7.5 h in dry acetonitrile (35 ml) in the presence of anhydrous sodium carbonate (0.47 g, 4.4 mmol). The orange-brown solid residue obtained after filtration and evaporation, when subjected to flash column chromatography on alumina (neutral, 10% deactivated) in CH_2Cl_2:Et_2O, gave a yellow solid from a yellow-green band on the column. Recrystallisation from ethyl acetate gave ethyl 3-oxo-3H-pyrrolo[2,1,5-de]quinolizine-1-carboxylate (33a) (0.42 g, 79%) as yellow needles, m.p. 166-167°C (lit.[6] m.p. 166-167°C); infrared and ^1H n.m.r. spectra identical with those of the specimen reported previously[6].

Reaction of 1-hydroxyquinolizinylium bromide with ethyl propiolate in the presence of 9,10-phenanthraquinone

Under a dry nitrogen atmosphere, 1-hydroxyquinolizinylium bromide monohydrate (1.00 g, 4.0 mmol), ethyl propiolate (0.58 g, 6.0 mmol) and 9,10-phenanthraquinone (0.86 g, 4.0 mmol) were stirred and refluxed in dry acetonitrile (60 ml) in the presence of anhydrous sodium carbonate (0.86 g, 8.0 mmol). After 5 h, the reaction solution was cooled, filtered and evaporated to give a brown solid (2.1 g) which was subjected to m.p.l.c. on a column (200 x 35 mm) of t.l.c. alumina (Fluka type G), eluting with ether-dichloromethane. The following solids were isolated [listed in order of Rf on silica t.l.c. in CH_2Cl_2:Et_2O (4:1)]:

(i) an orange-yellow solid which was recrystallised from ethyl acetate to give ethyl 2-(7-oxo-5,7-dihydrobenz[c,d]oxepin-5-yl)-5-oxo-5H-pyrrolo[2,1,5-de]quinolizine-1-carboxylate [CPQ(B), (234)] (0.018 g, 1%) as orange-yellow prisms, m.p. 262-265°C (Found: M^+ 449.1254. $C_{28}H_{19}NO_5$ requires 449.1263); $\bar{\nu}$max 1720, 1685 and 1635 (C=O) cm^{-1}; λmax (EtOH) 221, 244, 287, 303, 352, 442 sh and 467 nm ($\log_{10}\varepsilon$ 4.60, 4.45, 4.39, 4.38, 3.38, 4.12 and 4.46), δ_H and δ_C Table 25;

(ii) an orange-yellow crystalline solid which was recrystallised from ethyl acetate to give ethyl 5-oxo-5H-pyrrolo[2,1,5-de]quinolizine-1-carboxylate (182) (0.026 g, 3%) as orange-yellow needles, m.p. 165-167°C (lit.[6] m.p. 167-168°C); $\bar{\nu}$max 1690 (C=O), 1645(C=O) cm^{-1};

^{1}H n.m.r. spectrum identical with that of the specimen reported previously[6];

(iii) an orange-yellow solid, which was recrystallised from ethyl acetate to give ethyl 2-(9,10-dihydro-9-hydroxy--10-oxo-phenanthrene-9-yl)-5-oxo-5H-pyrrolo[2,1,5-de]--quinolizine-1-carboxylate [CPQ(A);(223)] (0.161 g, 9%) as yellow needles, m.p. 245-248°C (Found: C, 74.9; H, 4.3%; N, 3.1%; M^+ 449.1265. $C_{28}H_{19}NO_5$ requires C, 74.8; H, 4.3; N, 3.1%; M^+ 449.1263); $\bar{\nu}$max 3200 br (OH), 1690 (C=O), 1630 (C=O) cm^{-1}; λmax (EtOH) 218, 245, 272 i, 284, 305, 330 i, 350 i, 442 sh, and 468 nm ($\log_{10}\varepsilon$ 4.28, 4.61, 4.38, 4.47, 4.31, 3.88, 3.61, 4.11 and 4.43), δ_H and δ_C Table 24.

Attempts to prepare an adduct from 9,10-phenanthraquinone and ethyl propiolate in the presence of a base

Phenanthraquinone (1 equiv.) and ethyl propiolate (1.5 equiv.) were heated under reflux in acetonitrile under nitrogen, in the presence of various bases.

a) In the presence of anhydrous sodium carbonate no change was detected by t.l.c. after 8 h.

b) In the presence of anhydrous potassium carbonate and 18-crown-6 some reaction occurred but work-up after 2.5 h and preparative t.l.c. gave only traces of products, none of which was identifiable as an adduct of the starting materials.

c) In the presence of sodium ethoxide, the solution became dark brown. Work-up after 4 h gave a brown oil which was shown by t.l.c. to contain at least 7 components. Preparative t.l.c. yielded only traces of products,

none of which was identifiable as an adduct.

Attempted reaction of ethyl 5-oxo-5H-pyrrolo[2,1,5-de]-quinolizine-1-carboxylate with 9,10-phenanthraquinone

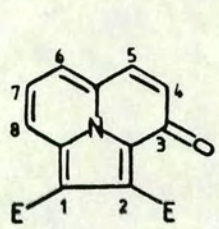
The cyclazinone (0.010 g, 0.04 mmol), 9,10-phenanthraquinone (0.009g, 0.04 mmol) and anhydrous sodium carbonate (0.009 g, 0.08 mmol) were stirred together in dry acetonitrile (1.5 ml) and refluxed under nitrogen.

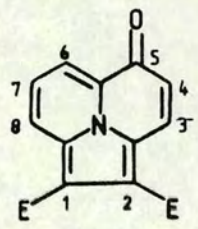
After 6 h, t.l.c. showed that no reaction had occurred, and after a further 7 h the heating was stopped since no formation of the products CPQ(A) or CPQ(B) was evident. No work-up was performed on this small scale reaction.

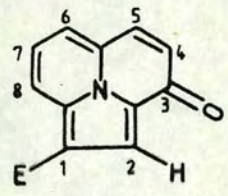
Conversion of ethyl 2-(9,10-dihydro-9-hydroxy-10-oxo--phenanthrene-9-yl)-5-oxo-5H-pyrrolo[2,1,5-de]quinolizine--1-carboxylate [CPQ(A),(233)] into ethyl 2-(7-oxo-5,7--dihydrodibenz[cd]oxepin-5-yl)-5-oxo-5H-pyrrolo[2,1,5-de]--quinolizine-1-carboxylate [CPQ(B),(234)]

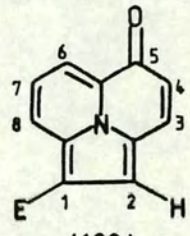
CPQ(A) (0.007 g, 0.02 mmol) was refluxed with anhydrous sodium carbonate (0.040 g) in dry acetonitrile (1 ml) under dry nitrogen. After 3.5 h, t.l.c. revealed that two spots were present, and these were identified as starting material CPQ(A) and the isomeric product CPQ(B) by comparison on t.l.c. with authentic samples of these materials. After six hours refluxing, both species were still present and the conversion of CPQ(A) to CPQ(B) was thus only partial. No work-up was performed for this small scale experiment.

Table 16. ^{1}H n.m.r. spectra of compounds (33a), (181), (182) and (183)


(183)


(181)


(33a)


(182)

E = CO_2Et

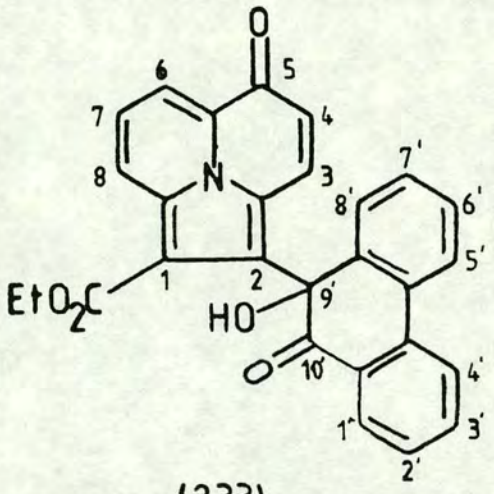
δ/H[a)b)]	H-1	2	3	4	5	6	7	8	Coupling J/Hz
(183)[c)]	[1.47] [4.58]	[1.42] [4.44]	-	7.29(d)	7.91(d)	7.80(dd)	7.81(dd)	8.76(dd)	$J_{4,5}$ 9.9 $J_{6,7}$ indet. $J_{7,8}$ indet. e) $J_{6,8}$ indet. J_{gem} 7.1
(181)[c)]	[1.44] [4.47]	[1.46] [4.57]	8.26(d)	7.12(d)	-	8.56(dd)	7.94(dd)	8.84(dd)	$J_{3,4}$ 10.0 $J_{6,7}$ 7.6 $J_{7,8}$ 8.6 $J_{6,8}$ 1.1 J_{gem} 7.1
(33a)[c)]	[1.45] [4.45]	8.47(s)	-	7.36(d)	7.94(d)	7.8	7.8	8.78(dd)	$J_{4,5}$ 9.9 $J_{6,7}$ indet. $J_{7,8}$ indet. e) $J_{6,8}$ indet. J_{gem} 7.1
(182)[d)]	[1.46] [4.47]	7.98(s)	8.08(d)	7.08(d)	-	8.56(dd)	7.92(t)	8.87(dd)	$J_{3,4}$ 9.8 $J_{6,7}$ 7.6 $J_{7,8}$ 8.4 $J_{6,8}$ 1.2 J_{gem} 7.1

a In $CDCl_3$ b Values in parenthesis indicate substituent shift

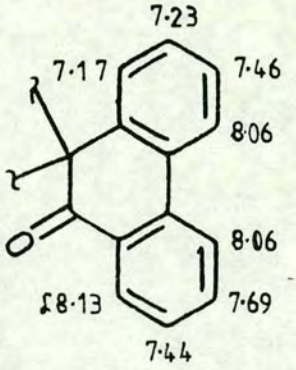
c At 200MHz d At 80 MHz

e 2nd order effects

Table 24A ^{1}H n.m.r. data for compound (233)



(233)



(233A)

δ[a]	m	No. of H	Results of decoupling expts.[c]										Assignment
8.83	dd	1H	hν	+				+					H-8
8.55	dd	1H	+	hν	d)			+					H-6
8.50	d	1H		d)	hν							+	H-3
8.13	dd	1H				hν	d)		+				H-1'
8.06	2xbr.d.	2H				d)	hν		+	?			H-4'/5'
7.91	dd	1H	+	+	?			hν					H-7
7.69	dt	1H				+	+		hν				H-3'
7.46	dt	1H					+			+	?		H-6'
7.44	dt	1H				+			+				H-2'
7.23	dt	1H					+			hν	?		H-7'
7.17	dd	1H								?	hν		H-8'
6.97	d	1H			+							hν	H-4
4.61[b]	br.s	1H											OH
4.08	dq	1H											>CH-H ester
4.01	dq	1H											>CH-H ester
1.07	t	3H											CH_3 ester

Coupling constants: $J_{3,4}$ 10.2; $J_{6,7}$ 7.7; $J_{6,8}$ 1.2; $J_{7,8}$ 8.5; J_{vic} 7.1; J_{gem} 10.8 Hz

a) 360 MHz in $CDCl_3$ b) Peak removed on D_2O shake

c) Decoupling experiments; hν indicates irradiation frequency: + indicates definite positive effect; ? indicates possible effect (very small)

d) Indicates collapse of signal caused by close proximity to irradiation point.

Table 24B. ^{13}C n.m.r. data for (233)

δ[a]	Peaks in DEPT Spectrum		Assignment
	$p\phi = \pi/2$[b]	$p\phi = 3\pi/4$[c]	
13.9		+	$sp^3 CH_3$
60.8		-	$sp^3 CH_2$
78.0			$sp^3 COH$
110.3			$sp^2 C$
118.4	+	+	$sp^2 CH$
122.2			$sp^2 C$
123.2	+	+	$sp^2 CH$
123.7	+	+	$sp^2 CH$
123.8	+	+	$sp^2 CH$
124.6	+	+	$sp^2 CH$
126.6	+	+	$sp^2 CH$
128.5			$sp^2 C$
128.7	+	+	$sp^2 CH$
128.8	+	+	"
129.0	+	+	"
129.4	+	+	"
129.5	+	+	"
130.3			$sp^2 C$
132.6	+	+	$sp^2 CH$
133.7			$sp^2 C$
134.6	+	+	$sp^2 CH$
136.3			$sp^2 C$
137.7			2 x $sp^2 C$[d]
140.1			$sp^2 C$
163.6			$sp^2 C{=}O$ (ester)
175.7			$sp^2 C{=}O$ (cyclazine C-5
194.1			$sp^2 C{=}O$ Ar'$\underline{C}{=}O$

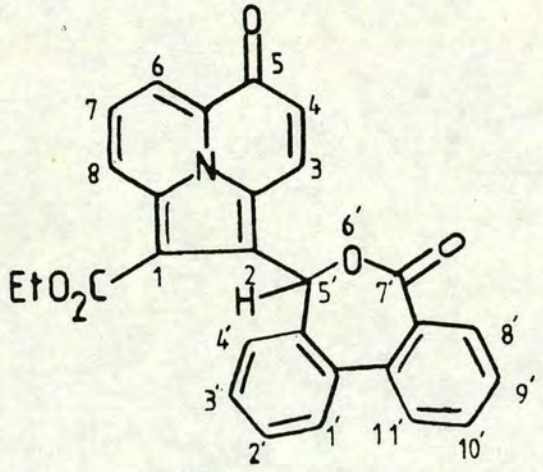
a) At 90.56 MHz in $CDCl_3$

b) CH only (+)

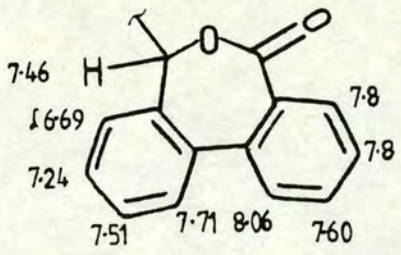
c) CH_3/CH (+ve); CH_2 (-ve); no quaternaries

d) Separated lines visible from expansion of ^{13}C n.m.r. region.

Table 25A ^{1}H n.m.r. data for compound (234)



(234)



(234A)

δ /ppm.

δ[a),b)]	m	No. of H	Results of decoupling expts.[c)]										NOE expts.[e)]		Assignment
8.93	dd	1H	hv	d)	+	+									H-8
8.85	d	1H	d)	hv			+							1%	H-3
8.63	dd	1H	+		hv	+									H-6
8.06	ddd	1H				d)		hv	+						H-11'
7.98	dd	1H	+		+	hv		d)							H-7
7.73-7.80	m	2H						+	+						H-8'/9'
7.71	dd	1H								+	+				H-1'
7.60	ddd	1H						+	hv	d)					H-10'
7.51	td	1H							d)	hv	+	+		hv	H-2'
7.46	s	1H											2%		H-5'
7.24	td	1H					d)		?	+	hv	+			H-3'
7.16	d	1H		+			hv				d)				H-4
6.69	dd	1H								+	+	hv		?	H-4'
4.11	dq	1H													CH-H(ester)
4.10	dq	1H											6.8%		CH-H(ester)
0.95	t	3H											hv		CH_3 (ester)

Coupling constants: $J_{3,4}$ 10.1; $J_{6,7}$ 7.7; $J_{6,8}$ 1.2; $J_{7,8}$ 8.5; J_{vic} 7.1; J_{gem} 10.8 Hz

a) 360 MHz spectrum in $CDCl_3$.

b) No change in spectrum when D_2O shake performed.

c) Decoupling experiments; hv indicates irradiation frequency; + indicates definite positive effect; ? indicates possible effect (very small).

d) Indicates collapse of signal caused by close proximity to irradiation point.

e) N.O.E. experiments; hv indicates irradiation frequency; % enhancements given.

Table 25B ^{13}C n.m.r. data for compound (234)

δ [a]	Peaks in DEPT Spectrum		Assignment
	$p\phi = \pi/2$ [b]	$p\phi = 3\pi/4$ [c]	
13.6		+	$sp^3 CH_3$
60.5		-	$sp^3 CH_2$
75.6	+	+	sp^3 CH-O
109.1			sp^2 C
118.7	+	+	sp^2 CH
120.7			sp^2 C
123.8	+	+	sp^2 CH
125.2	+	+	"
125.6	+	+	"
126.9	+	+	"
128.6	+	+	"
128.7	+	+	"
128.9	+	+	"
129.0	+	+	"
129.8	+	+	"
130.1			sp^2 C
131.3			"
131.7	+	+	sp^2 CH
132.9	+	+	"
133.0	+	+	"
133.7			sp^2 C
137.3			"
137.4			"
138.0			"
138.2			"
163.2			sp^2 C=O (ester)
168.8			sp^2 C=O (lactone)
175.9			sp^2 C=O (cyclazine C-5)

a) AT 90.56 MHz in $CDCl_3$

b) CH only +ve

c) CH/CH_3 (+ve); CH_2 (-ve); no quaternaries.

U.V. SPECTRUM - COMPARISON OF COMPOUNDS (233)/[CPQA] AND (182) WITH A STANDARD IN ETHANOL.

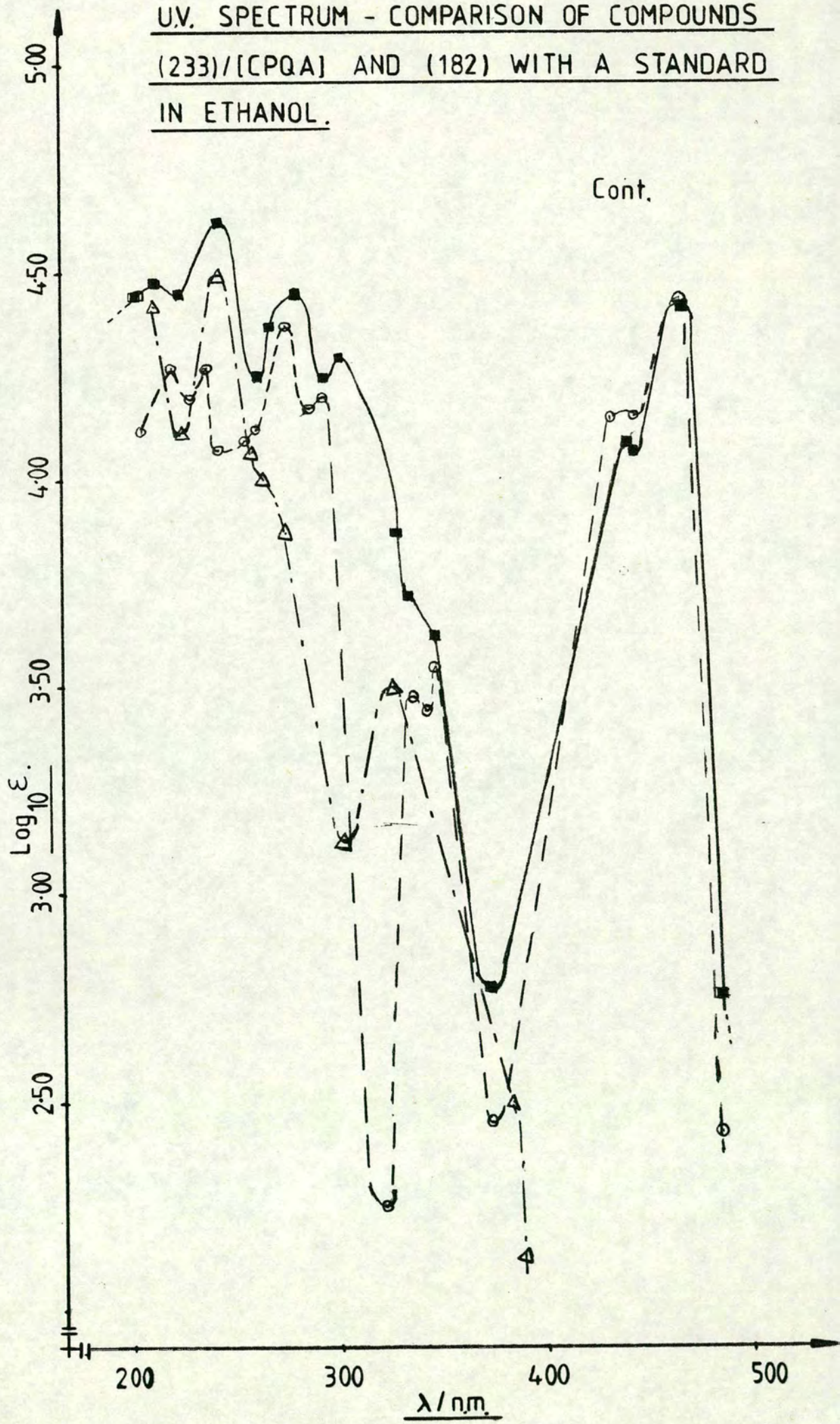
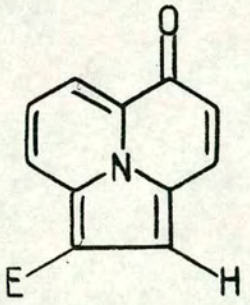
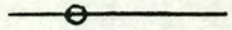


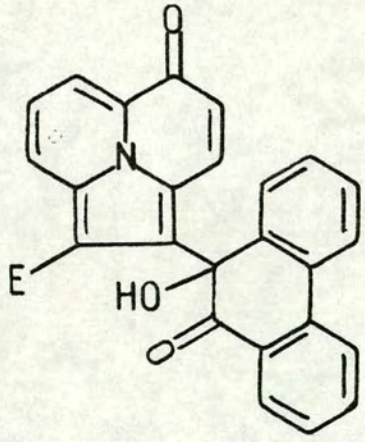
FIG. 7

UV SPECTRUM - FIG.7 CONT.

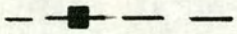


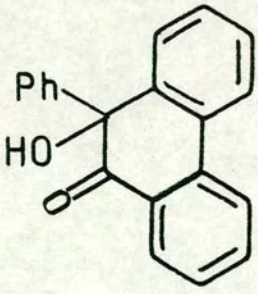
(182)



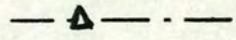


(233)
CPQA





(233X)



SECTION IV

BIBLIOGRAPHY

BIBLIOGRAPHY

1. a) V. Boekelheide and R.J. Windgassen, J.Amer.Chem.Soc., 1958, 80, 2020.

b) R.J. Windgassen, W.H. Saunders and V. Boekelheide, Ibid, 1959, 81, 1459.

2. M.A. Jessep and D. Leaver, J.Chem.Soc., Perkin Trans. I, 1980, 1319.

3. a) I.U.P.A.C. "Nomenclature of Organic Chemistry": Sections A, B and C, Butterworths, London, 1969.

b) A.D. McNaught, Adv.Heter.Chem., 1976, 20, 176.

4. a) W. Flitsch and U. Krämer, Adv.Heter.Chem., 1978, 22, 321.

b) W. Flitsch in "Comprehensive Heterocyclic Chemistry", Pergamon Press, Oxford, 1984, 4 (Pt. 3), p. 478 and 443, Edited by C.W. Bird and G.W.H. Cheeseman.

c) A. Taurins, Heterocyclic Chemistry, 1977, 30, 245.

d) K. Matsumoto, T. Uchida and J. Yamaguchi; Yuki Gosei Kagaku Kyoshaishi, 1977, 35, 739; (Chem.Abs., 1978, 88, 37642).

5. S.J. Lee and J.M. Cook, Heterocycles, 1983, 20, 87.

6. D. Farquhar, T.T. Gough, D. Leaver, J.F. Miller, J.W. Dick and M.A. Jessep, J.Chem.Soc., Perkin Trans. I, 1984, 2553.

7. R.M. Acheson and D.A. Robinson, J.Chem.Soc. (C), 1968, 1633.

8. Original proposal of ion - see footnote of ref. 1b).

9. a) O. Diels and F. Möller, Justus Liebigs Ann.Chem., 1935, 45, 516.

10. R.M. Acheson and R.S. Feinberg, J.Chem.Soc., Chem. Commun., 1965, 342.

11. W.K. Gibson, D. Leaver, J.E. Roff and C.W. Cumming, J.Chem.Soc., Chem.Commun., 1967, 214.

12. J.W. Dick, W.K. Gibson, D. Leaver and J.E. Roff, J.Chem.Soc., Perkin Trans. I, 1981, 3150.

13. Ref 6., p.2553.

14. G.M. Saunders, M. van Dijk and H.C. van der Plas, Heterocycles, 1981, 15, 213.

15. E. Bergmann, J.Amer.Chem.Soc., 1952, 74, 1075.

16. V. Boekelheide and W.G. Gall, J.Org.Chem., 1954, 19, 499.

17. a) H.V. Hansen and E.D. Amstutz, J.Org.Chem., 1963, 28, 393.

    b) V. Boekelheide, H. Fritz, J.M. Ross and H.X. Kaempfen, Tetrahedron, 1964, 20, 33.

18. D. Leaver and J.D.R. Vass, J.Chem.Soc., 1965, 1629.

19. G.R. Underwood, J.Org.Chem., 1968, 33, 1313.

20. R.D. Brown and B.A.W. Coller, Mol.Phys., 1959, 2, 158.

21. a) W.K. Gibson and D. Leaver, J.Chem.Soc. (C), 1966, 324.

    b) W.K. Gibson and D. Leaver, J.Chem.Soc., Chem.Commun., 1965, 11.

    c) R.P. Cunningham, D. Farquhar, W.K. Gibson and D. Leaver, J.Chem.Soc. (C), 1969, 239.

22. a) D. Farquhar and D. Leaver, J.Chem.Soc., Chem.Commun., 1969, 24.

b) D. Farquhar, T.T. Gough and D. Leaver, J.Chem.Soc., Perkin Trans. I, 1976, 341.

23. a) R.M. Acheson and D.M. Goodall, J.Chem.Soc., 1964, 3225.

b) R.M. Acheson, S.J. Hodgson and R.G.M. Wright, J.Chem.Soc., Perkin Trans. I, 1976, 1911.

24. G.G. Abbott, D. Leaver and K.C. Mathur, J.Chem.Res., 1978; (S), 224; (M), 2850.

25. a) M.H. Palmer, D. Leaver, J.D. Nisbet, R.W. Millar and R.E. Egdell, J.Mol.Str., 1977, 42, 85.

b) A. Sabljic and N. Trinajstić, J.Mol.Str., 1978, 49, 415.

26. T.T. Gough, Ph.D. Thesis, Univ. of Edinburgh, 1972

27. a) W. Leupin and J. Wirz, J.Amer.Chem.Soc., 1980, 102, 6068.

b) W. Leupin, S.J. Berens, D. Magde and J. Wirz, J.Phys.Chem., 1984, 88, 1376.

28. a) B.A. Hess, L.J. Schaad and C.W. Holyoke, Tetrahedron, 1972, 28, 3657.

b) M.J.S. Dewar and N. Trinajstić, J.Chem.Soc. (A), 1969, 1754.

c) F. Gerson, J. Jachviowicz and D. Leaver, J.Amer. Chem.Soc., 1973, 95, 6702. F. Gerson, Helv.Chim. Acta., 1966, 49, 1463.

29. W. Leupin, D. Magde, G. Persy and J. Wirz, J.Amer.Chem. Soc., 1985, 108, 17.

30. M.A. Rossman, N.J. Leonard, S. Urano and P.R. Le Breton, J.Amer.Chem.Soc., 1985, 107, 3884.

31. L. Gmelin, Ann., 1835, 15, 252.

32. a) L. Pauling and R. Sturdivant, Proc.Nat.Acad.Sci., 1937, 23, 615.

b) C.E. Redemann and J.H. Lucas, J.Amer.Chem.Soc., 1940, 62, 842.

33. a) P. Mrazek, Ph.D. Thesis, Univ. of Vienna, 1946.

b) J.L. Van Winkle, French Pat., 1 316734, 1963/ U.S. Patent 3 112 314, 1963. J.L. Van Winkle, J.D. McClure and P.H. Williams, J.Org.Chem., 1966, 31, 3300

34. K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, Chem. Pharm. Bull., 1976, 24, 2270.

35. H. Gotou, K. Kurata, Y. Tominaga and Y. Matsuda, J.Org.Chem., 1985, 50, 4028.

36. D. Leaver, Pure and App. Chem.,1986, 58, 143. [Synopsis of a lecture given by D. Leaver at the I.U.P.A.C./R.S.C. 5th International Symposium on novel aromatic compounds, St. Andrews, July 1985].

37. D. Leaver and R. McGuire, Univ. of Edinburgh, 1983, unpublished results..

38. N. Petragnani and M. Yonashiro, Synthesis, 1982, 521.

39. Review: P.P. Fu and R.G. Harvey, Chem.Rev., 1978, 78, 317.

40. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, New York, 1967, 1, 128.

41. W.D. Hooper, Rev. Pure and App. Chem., 1969, 19, 221.

42. H.J. Dauben, L.R. Honnen and K.R. Harmon, J.Org. Chem., 1960, 25, 1442.

43. D. Leaver, Univ. of Edinburgh, unpublished results.

44. M.A. Barton, G.W. Kenner and R.C. Sheppard, J.Chem. Soc. (C), 1966, 1061.

45. a) R.F. Hudson and C. Brown, Acc.Chem.Res., 1972, 5, 204

b) F. Ramirez and N.B. Desai, J.Amer.Chem.Soc., 1960, 82, 2652. Ibid, 1963, 85, 3252. W.C. Hamilton, S.J. La Placa, F. Ramirez and C.P. Smith, J.Amer. Chem.Soc., 1967, 89, 2268.

46. a) F. Johnson, J.P. Panella and A.A. Carlson, J.Org. Chem., 1962, 27, 2241.

b) F. Johnson, J.P. Panella, A.A. Carlson and D.H. Hunneman, J.Org.Chem., 1962, 27, 2473.

47. J. Becher, Synthesis, 1980, 662.

48. V.N. Mikhailova, V.P. Yurevich and A.D. Bulat, Zh. Org. Khim., 1971, 7, 562.

49. J.A. Van Allan and G.A. Reynolds, J.Org.Chem., 1963, 28, 1022.

50. E.B. Knott, J.Chem.Soc., 1955, 916 and seq.

51. a) A. Eschenmoser, Quart.Rev., 1970, 24, 366.

b) M. Roth, P. Dubs, E. Götschi and A. Eschenmoser, Helv.Chim.Acta., 1971, 54, 710.

52. a) B.S. Pedersen, S. Scheibye, N.H. Nilsson and S.-O. Lawesson, Bull.Soc.Chim.Belg., 1978, 87, 223.

b) S. Scheibye, B.S. Pedersen and S.-O. Lawesson, Bull.Soc.Chim.Belg., 1978, 87, 229.

53. B.S. Pedersen, S. Scheibye, K. Clausen and S.-O. Lawesson, Bull.Soc.Chim.Belg., 1978, 87.

54. H. Fritz, P. Hag, S.-O. Lawesson, E. Logemann, B.S. Pedersen, H. Sauter, S. Scheibye and T. Winkler, Bull.Soc.Chim.Belg., 1978, 87, 525.

55. Y. Yamashita, D. Suzuki and M. Masumura, Heterocycles, 1984, 22, 705.

56. a) B.T. Gillis and P.E. Beck, J.Org.Chem., 1962, 27, 1947; Ibid, 1963, 28, 3177.

b) O. Diels, J.H. Blom and W. Koll, Ann., 1925, 443, 242.

57. a) J.M. Cinnamon and K. Weiss, J.Org.Chem., 1961, 26, 2644.

b) (i) B. Franzus and J.H. Surridge, J.Org.Chem., 1962, 27, 1951.

(ii) B. Franzus, Ibid, 1963, 28, 2954;

(iii) B. Franzus and W.A. Thaler, Ibid, 1964, 29, 226.

58. W.E. Stewart and T.H. Siddal, Chem.Rev., 1970, 70, 517.

59. a) L.A. Carpino, P.H. Terry and P.J. Crowley, J.Org. Chem., 1961, 26, 4336.

b) D. Mackay, C.W. Pilger and L.L. Wong, J.Org.Chem., 1973, 38, 2043.

c) D.M. Stout, T. Takaya and A.I. Meyers, J.Org.Chem., 1975, 40, 563.

60. J. Nakayama, O. Simamura and M. Yoshida, J.Chem.Soc., Chem. Commun., 1970, 1222.

61. F.M. Beringer and S. J. Huang, J.Org.Chem., 1964, 29, 445.

62. W. Kirmse, "Carbene Chemistry", Academic Press, London, 2nd Edition, 1971, p.381 and p.387.

63. (i) A.J. Hubert, A.F. Noels, A.J. Anciaux and P. Teyssié, Synthesis, 1976, 600;

(ii) A.J. Anciaux, A.J. Hubert, A.F. Noels, N. Petiniot and P. Teyssié, J.Org.Chem., 1980, 45, 695.

64. M.P. Doyle, D. Van Leusen and W.H. Tamblyn, Synthesis, 1981, 787.

65. Ref. 62, p.396.

66. (i) P.D. Bartlett, G.D. Mendenhall and D.L. Durham, J.Org.Chem., 1980, 45, 4269;

(ii) P.D. Bartlett and C.M. Lonzetta, J.Amer.Chem.Soc., 1983, 105, 1984.

67. E. Santaniello, A. Manzocchi and C. Farachi, Synthesis, 1980, 563.

68. E.J. Corey and G. Schmidt, Tetrahedron Letts., 1979, 399.

69. C.J.M. Stirling, "Radicals in Organic Chemistry", Oldbourne Press, London, 1965, p.61.

70. A.I. Vogel, "A Textbook of Practical Organic Chemistry (Incl. Qualitative Organic Analysis)", Longmans, London, 1956, p.611.

71. G. Wilkinson, F.G.A. Stone and E.W. Abel, Comprehensive Organometallic Chemistry, Pergamon Press, Oxford, 1982, 8, 1037.

72. a) J. Ferraris, D.O. Cowan, V. Walatka and J.H. Perlstein, J.Amer.Chem.Soc., 1973, 95, 948.

b) Review: D.O. Cowan and F. M. Wlygnd, Chem. and Eng. News, 1986, July 21, p.28.

73. a) C.N.R. Rao, "Chemical Applications of I.r. Spectroscopy", Academic Press, New York, 1963, p.268.

b) S. Patai, "The Chemistry of Functional Groups: The Chemistry of the Cyano group", Interscience, London, 1970, p.194, Edited by Z. Rappoport.

74. S.F. Mason, J.Chem.Soc., 1957, 5010.

75. M.H. Palmer, "The Structure and Reactions of Heterocyclic Compounds", Arnold Press, London, 1967, p.106.

76. P.A. Claret and A.G. Osborne, "Heterocyclic Compounds", Quinolines II, J. Wiley and Sons, Bristol, 1982, 32, p.34, edited by G. Jones; and references therein.

77. (i) M. Uno, K. Seto and S. Takahashi, J.Chem.Soc., Chem.Commun., 1984, 932.

(ii) M. Uno, K. Seto, M. Masuda, W. Ueda and S. Takahashi, Tetrahedron Letts., 1985, 26, 1553.

78. H. Suzuki, T, Kobayashi and O. Osuka, Chem.Letts., 1983, 589.

79. J.T. Shaw, K.S. Kyler and M.D. Anderson, J.Het.Chem., 1977, 14, 679.

80. P.A. Duke, A. Fozard and G. Jones, J.Org.Chem., 1965, 30, 526 .

81. A. Fozard and G. Jones, J.Chem.Soc., 1963, 2203 .

82. V.F. Bohlmann, N. Ottowa and R. Keller, Jus.Lieb.Ann., 1954, 587, 162 .

83. V. Boekelheide and J.P. Lodge, J.Amer.Chem.Soc., 1951, 73, 3681 .

84. D. Farquhar, G.G. Abbot and D. Leaver, Univ. of Edinburgh, unpublished results .

85. H.C. Brown, "Organic Synthesis via Boranes", Wiley, New York, 1975, p.191 (with techniques by G.W. Kramer, A.B. Levy and M.M. Midland).

86. A.I. Vogel, "Elementary Practical Organic Chemistry: Part I, Small Scale Separations", Longmans, London, 2nd Edition, 1966, p.299.

87. a) J.P. Supniewski and P.L. Salzberg, Org.Synth., 8, 4 .
b) E. Rietz, Org.Synth., 24, 96 .

88 (i) T. Zincke, Ann., 1904, 330, 361.
(ii) T. Zincke, G. Heuser and W. Möller, ibid, 1904, 333, 296 .

89. "Dictionary of Organic Compounds", Eyre and Spottiswoode, London, 4th Edn., 1971, Edited by R. Stevens.

90. L.M. Harwood, Aldrichimica Acta, 1985, 18/1. 25 .

91. J. Elks and D.H. Hey, J.Chem.Soc., 1943, 441 .

92. K.C. Mathur, Ph.D. thesis, Univ. of Edinburgh, 1969 .

93. L.F. Fieser and E.B. Hershberg, J.Amer.Chem.Soc., 1940, 62, 1640.

94. "Handbook of Tables for Organic Compound Identification", CRC Press, Ohio, 3rd Edn., 1967, comp. by Z. Rappoport.

95. a) F.R. Hartley, Organometallic Chem., Rev., 1970, A6, 119.

b) A. Schoenberg, I. Bartoletti and R.F. Heck, J.Org.Chem., 1974, 39, 3318.

96. J. Meili and J. Seibl, Org.Mass.Spectr., 1984, 19, 581.